Towards personalized treatment for patients with bone metastases

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Towards personalized treatment for patients with bone metastases
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Towards personalized treatment for patients with bone metastases

Op weg naar een op het individu gerichte behandeling voor patiënten met botmetastasen

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

General introduction and thesis outline

BONE METASTASES

Bone metastases are a common manifestation of advanced cancers as approximately one third of patients with cancer develop bone metastases during the course of their disease [1]. Bone is the preferred site for breast and prostate cancer metastases, but many other tumors including lung and renal cell carcinoma colonize the skeleton. Bone metastases are classified as osteolytic (*ie,* focal break down of bone via increased bone resorption, or as osteoblastic (*ie,* bone formation overcomes bone resorption) [2]. This classification represents two extremes of a continuum as patients can have both osteolytic, osteoblastic or mixed bony lesions. Pain is a common and debilitating consequence of bone metastases. It strongly interferes with quality of life and daily functioning, and often requires hospitalization. Furthermore, bone metastases may cause pathological fractures, anemia and symptomatic hypercalcaemia. Spinal metastases have a unique clinical position as these lesions can present with a paraspinal or epidural soft tissue mass, compressing the spinal cord and nerve roots. As a result, patients with spinal metastases may have severe neuropathic pain with (impending) associated neurological deficits [3]. The presence of metastases in bone is a poor prognostic sign: once tumors metastasize to the skeleton, patients are considered incurable [4]. The median survival of patients with bone metastases is less than seven months but survival ranges broadly [5, 6]. For patients suffering from metastatic disease with multiple organs involved in poor clinical condition, survival is measured in weeks, whereas median survival can be more than five years for patients with skeletal metastases only [7]. In general, for patients with bone metastases, the main challenge is to improve the quality of the patient's remaining life.

MANAGEMENT OF CANCER INDUCED BONE PAIN

Proper care of patients with bone metastases requires multidisciplinary effort and attention among the general practitioners, radiologists, radiation oncologists, medical oncologists, surgeons, pain medicine specialists, and palliative care professionals. For cancer pain in general, the cornerstone of treatment is the 'analgesic ladder' of the World Health Organization, starting with non-opioid analgesics including paracetamol and non-steroidal anti-inflammatory drugs [8]. It is common to omit the next step (*ie*, weak opioids) and proceed with strong opioids, which are mainstay in the treatment of cancer-induced bone pain [9]. If neuropathic pain is present, tricyclic antidepressants (*eg*, nortriptyline) or calcium channel a2-d ligand (either gabapentin or pregabalin) are usually prescribed in addition to opioids [10]. Once initial treatment has been started, further causal treatment options are available in specialist services. Patients might be referred to medical oncology for hormonal or chemotherapy, to nuclear medicine for radioisotope treatment, and to radiotherapy for local treatment [11, 12]. Other, not widely available local treatment modalities for bone metastases include High Intensity Focused Ultrasound (HIFU), radiofrequency ablation, and cryotherapy but these techniques are still limited by technological and clinical challenges [2, 13]. Bisphosphonates can be prescribed to reduce pain and the risk of

skeletal related events [14]. Another potential agent in the prevention of skeletal related events is denosumab, a monoclonal antibody that specifically inhibits receptor activator of nuclear factor κ B ligand, inhibiting osteoclast activity that results in tumor-induced bone destruction [15]. In patients with a good performance status and (impending) pathological fractures, surgical stabilization followed by radiotherapy, is the preferred treatment option [16, 17]. Traditionally for spinal fractures, surgical stabilization is performed through open procedures, which are associated with significant blood loss, lengthy hospital stays, and substantial complication rates [18]. In recent years, novel minimally invasive treatment options have been developed aiming to achieve comparable clinical outcomes but with decreased perioperative morbidity [19]. Minimally invasive surgery has been shown to be safe and feasible with good clinical results [20, 21]. Important and often overlooked aspects in the management of bone pain include non-medical interventions, such as behavior modifications and the use of appropriate movement aids [22].

CONVENTIONAL PALLIATIVE RADIOTHERAPY FOR BONE METASTASES

Conventional radiotherapy is the cornerstone of the management of bone metastases, which successfully provides palliation of painful bone metastasis. Palliative radiotherapy is time efficient and has been associated with very few side effects. There is extended evidence about optimal radiation treatment schedules in the palliation of bone metastases. Most studies show that there is no significant difference in terms of pain relief between short courses of radiotherapy using a larger fraction sizes (single fraction schedule) and longer courses giving a higher dose at a smaller dose per fraction (multiple fractions schedule) [23–25]. Accordingly, a radiation dose-response relationship for doses above 8 Gy has not been established. Conventional radiotherapy, whether delivered in single fraction or multiple fractions, is moderately effective. Around 60% of patients who underwent conventional radiotherapy reported pain relief [23–25] and around 20% of the irradiated patients receives re-irradiation at the site of initial radiotherapy [26]. Complete pain response, as defined by the International Bone Metastases Consensus Working Party [27, 28] is even lower, and ranges from 0 to 23% of the patients [25]. Consequently, more than 40% of patients with bone metastases do not obtain sufficient pain relief after conventional radiotherapy. It is important to improve pain response, since patients whose pain responded to radiotherapy have a better quality of life compared to non-responders [29].

STEREOTACTIC BODY RADIOTHERAPY FOR BONE METASTASES

First pioneered in mainly brain radiotherapy, in 1995 the possibility of linear-accelerator based stereotactic body radiotherapy (SBRT) for spinal metastases was described [30]. SBRT tries to improve pain response by delivering a high-dose radiation precisely to the bone 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 [31]. Since then, despite the lack of level 1 evidence, multiple centers have attempted to pursue high-fraction conformal radiation delivery to spinal lesions. Various SBRT techniques have been described, mainly in retrospective single-institution series and a few prospective experimental trials, and the feasibility and safety of SBRT is well established [32]. Traditionally, stereotactic radiotherapy in metastatic bone disease is intended for patients with spinal metastases, but SBRT is increasing being applied in the treatment of extra-axial osseous metastases [33].

Currently, there are no recommendations for dose selection in spinal SBRT. Fractionation schemes vary from 12–24 Gy in one fraction, 20–27 Gy in two to three fractions, and 30–40 Gy in five fractions [34]. These doses create a substantial increase in the biologically effective dose as compared with conventional palliative fractionation schemes. Early reports of SBRT using relatively low doses detected a high incidence of failure, which was attributed by the authors to the low radiation dose. These authors recommend a dose of at least 13 Gy [35], 14 Gy [36] or 15 Gy [37]. From a biological perspective, results from experimental studies suggest that SBRT fractionation schedules with at least 10 Gy per fraction or higher induce considerable larger antitumor efficacy than expected [38, 39]. Unlike conventional radiotherapy, no randomized study has been performed to identify the most effective hypofractionated regimen for spinal SBRT. Proponents of single fraction SBRT claim that doses of 15–20 Gy results in immediate apoptosis of tumor cells [40]. Generally, single SBRT is thought to be advantageous for bone metastases from radioresistant histologies [41–43]. In larger volume tumors, in tumors in close proximity to organs at risk and in the retreatment setting particularly, fractionated SBRT might be preferred, as fractionation takes advantage of normal tissue's enhanced ability to repair radiation-induced damage compared to tumor cells and makes use of reoxygenation between every fraction [34]. Furthermore, some suggested benefits of fractionated SBRT are that it may decrease the risk of pain flare [44], spinal cord myelopathy [45] and the occurrence of vertebral compression fractures [46].

COMPLICATIONS OF SBRT: VERTEBRAL COMPRESSION FRACTURES

Concern has been raised about the extreme dose-fractionation schemes and large biologically effective dose used in spinal SBRT, because of the increased risk for serious adverse events including vertebral compression fractures (VCF) [47]. The risk of VCF ranges from 10 to 39% [46], which is much higher in comparison with conventional radiotherapy where the risk of fracture ranges from 3.3% to 5% [25]. Management and prevention of VCF is a challenge because the metastatic disease lies within the spinal segment where the radiation dose is delivered. To date, four reports have detailed outcomes for VCF after spinal SBRT [48, 49] including a specific dosimetric analysis [46, 50]. The first dosimetric analysis showed a significant relation between dose per fraction and VCF: spinal segments treated with 20 Gy or more per fraction had a seven

times higher risk of VCF compared to those treated with less than 20 Gy [50]. The largest multi-institutional experience with spine SBRT reported a 1-year VCF cumulative incidence of 39% with ≥ 24 Gy/fraction, of 19% with 20–23 Gy/fraction, and of 10% with ≤ 19 Gy/fraction [46]. These results suggest that if the dose per fraction is reduced, the safety profile of spine SBRT with respect to VCF can be improved.

THE SET UP OF THE PRESENT COHORT FOR PATIENTS WITH BONE METASTASES

In the University Medical Center Utrecht, several new interventions for patients with bone metastases are being developed and evaluated: SBRT for spinal and extra-spinal metastases, MR-HIFU [51] and the MR-Linac [52]. We have set up the PRESENT cohort, where PRESENT stands for PRospective Evaluation of interventional StudiEs on boNe metastases. PRESENT includes all patients with bone metastases referred to the departments of radiotherapy and orthopedic surgery, and serves as a prospective cohort study. The PRESENT cohort is set up according to the 'cohort multiple Randomized Controlled Trial' (cmRCT) design, which allows for efficient, fast and pragmatic evaluation of multiple innovative interventions [53].

Effectiveness of new interventions, and their superiority (or at least non-inferiority) relative to standard treatments, should be evaluated in well-designed comparative studies. Generally, the randomized controlled trial (RCT) is regarded as the 'gold standard' for comparative clinical research. RCTs are challenged by a range of problems, including the long duration from conceptualization to inclusion, high rate of failure to recruit to target sample size, highly selective patient populations – and therefore limited generalizability of the results – and high costs [54]. The cmRCT was developed to address some of these problems [53, 55]. The basis of the cmRCT approach is an observational prospective cohort, consisting of patients with the same condition of interest, who undergo standard treatment. The patient characteristics are captured at baseline and clinical and patients reported outcome measures are captured at fixed time intervals. When a new intervention is ready for formal evaluation, eligible patients within the observational cohort are identified. From this so-called subcohort, some patients will be randomly selected to undergo the new intervention. The eligible patients, who are not randomly selected, will not be approached and undergo standard treatment. Outcomes of the selected patients who have been offered the new intervention will be compared with the outcomes of the patients who were not offered the intervention. Within this cohort, the same process can be simultaneously repeated for other interventions. Advantages of the cmRCT design include ongoing information as to the natural history of the condition and to treatment as usual, the ability to facilitate multiple simultaneous randomized evaluations, the improved comparability between trials and the patient-centered informed consent procedure.

PURPOSE AND OUTLINE OF THESIS

In this thesis different aspect of the radiation treatment of patients with bone metastases are explored, working towards a more individualized approach of these patients. First, using data from the PRESENT cohort, current effectiveness of conventional radiotherapy is evaluated and the outcomes from the patients in this unselected cohort are compared with outcomes from patients enrolled in randomized trials (*Chapter 2*). The association between patient and tumor characteristics and pain response in patients with bone metastases is investigated in *Chapter 3*. In *Chapter 4*, the predictive value of the Spinal Instability Neoplastic Score (SINS), as a marker for spinal instability, was explored in a multi-international cohort. The following two chapters address stereotactic radiotherapy technique: *Chapter 5* compares the inter-observer agreement in bone metastases delineated on different imaging modalities, and in *Chapter 6* a simultaneous integrated boost approach is described. In *Chapter 7*, outcomes after SBRT for bone metastases are summarized in a systematic review and meta-analysis, providing pooled estimates of pain response and local control rate. The results from the previous chapters are subsequently integrated in *Chapter 8*, in which the first randomized trial within the PRESENT cohort, the VERTICAL trial, is described. The methodological issues of conducting one RCT within a cohort is discussed in *Chapter 9*. The last chapters summarize (*Chapter 10*) and reflect on (*Chapter 11*) the outcomes of this thesis.

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CHAPTER 2

Evaluation of effectiveness of palliative radiotherapy for bone metastases: A prospective cohort study

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ABSTRACT

Background and Purpose

Radiotherapy is the standard local treatment for patients with painful bone metastases, but effectiveness has primarily been evaluated in trial populations. The aim of this study was to evaluate pain response to palliative radiotherapy in a prospective cohort of unselected patients with bone metastases.

Material and methods

Patients with painful bone metastases referred to the UMC Utrecht for radiotherapy and enrolled in the PRESENT cohort, were included in this study. For all patients, pain response to radiotherapy was assessed, and responders were defined as patients with a complete or partial pain response. Patients with stable pain scores, pain increase, or undetermined response were regarded non-responders. Pain scores obtained at baseline, and after 2, 4, 6, 8, and 12 weeks following radiotherapy were obtained. Pain response rates of the total treated population, as well as response rates of the assessable patients were calculated. To measure the percentage of remaining time spent with pain relief, the net pain relief (NPR) was calculated by dividing the period of pain relief by the period of survival.

Results

Of the 432 patients enrolled in this study, 262 patients (61%) experienced a complete or partial response. In the 390 assessable patients, this percentage was 67%. Median time to response was four weeks (range 1–15 weeks) and the NPR was 64%.

Conclusions

Compared to randomized trial populations, palliative radiotherapy in our unselected patients with bone metastases showed similar pain response rates (61%), with a reasonable duration of this effect.

INTRODUCTION

Many patients with cancer develop bone metastases, with pain as a common and severe consequence. Due to improved treatment options for primary tumors and subsequent longer survival, the number of patients with bone metastases is likely to increase. They represent a heterogeneous group with differences in tumor histology, extent of the disease, and expected survival. As the diagnosis of bone metastases often represents incurable disease, the main treatment goal is palliation of symptoms [1]. Adequate symptom management is important, as cancer-related pain negatively influences quality of life [2]. Palliative conventional radiotherapy constitutes the standard of care for patients with painful bone metastases, sometimes combined with other treatments such as change in pain medication, radiopharmaceuticals, or surgical stabilization. The best evidence regarding effectiveness of treatments is generally provided by randomized controlled trials. Systematic reviews of palliative radiotherapy trials for bone metastases showed a similar overall pain response rate in patients receiving single *vs.* multiple fractions with pooled pain response rates of 60% and 61% respectively [3, 4]. Of the patients experiencing a pain response, around 20% reported complete pain response [4]. Clinical trials usually use strict inclusion criteria, resulting in inclusion of selected patients, who are often not representative of the entire patient population. Restricted patient access to trials, and physician or patient resistance to randomization might lead to further selected recruitment [5]. What is more, trials in the metastatic setting or trials investigating radiation treatments are more likely to be classified as trials with slow recruitment, thereby increasing the risk of selected enrolment [6]. This limits the generalizability of the results of these trials as patients enrolled in clinical trials – also in trials investigating palliative research questions – are usually a (relatively) healthier subgroup of patients referred for treatment [7, 8]. Therefore, our aim was to study whether pain response rates from randomized trials are similar to those observed in patients with bone metastases treated in daily practice.

PATIENTS AND METHODS

Patients were retrieved from the prospective Prospective Evaluation of interventional StudiEs on boNe metastases (PRESENT) cohort, which includes patients with bone metastases referred to the departments of radiation oncology or orthopedic surgery at our center since June 2013 [9]. Within the PRESENT cohort, detailed information on tumor and treatment characteristics, imaging, vital status and patient reported outcomes are collected. The PRESENT cohort follows the cohort multiple randomized controlled trial (cmRCT) design and serves as an infrastructure for efficient and pragmatic (randomized) treatment evaluation [10]. In this context, patients give separate informed consent to be offered experimental interventions at random [11]. All patients with bone metastases are eligible for inclusion in PRESENT except for patients who are younger than 18 years, and/or incompetent to give informed consent. Prior to their first appointment with the radiation oncologist, patients are routinely asked to participate in PRESENT by a re-

searcher or research assistant. At enrollment, written informed consent for collection of baseline demographics, treatment characteristics, and clinical follow-up data is obtained. Patients are also asked to provide patient reported outcomes by filling out the Brief Pain Inventory (BPI, [12]), the EORTC QLQ-C15-PAL [13], the EORTC QLQ-BM22 [14], and the EQ-5D [15] at baseline, and 2, 4, 6, 8 weeks, 3 and 6 months after initial radiotherapy and every 6 months thereafter. The study protocol for PRESENT was approved by the Institutional Review and Ethics Board of the University Medical Center Utrecht, the Netherlands.

This study was performed after enrollment of the first 500 PRESENT patients. For the present analysis, we excluded patients who did not undergo radiotherapy (n=9), patients not having metastases from solid tumors (n=18), patients who underwent stereotactic radiotherapy (n=25), and patients with asymptomatic lesions (n=27). At our department, patients in good clinical condition with a limited number of bone metastases from favorable tumors are usually treated with long course (*ie,* 30 Gy in 10 fractions) radiotherapy, but the default radiotherapy schedule is single fraction radiotherapy of 8 Gy.

The primary endpoint was pain response between 2 and 12 weeks after radiation treatment. Patients reported their pain score on a scale from 0 (no pain) to 10 (worst imaginable pain) and the BPI item *worst pain in last three days* was used. In addition, analgesic use was recorded, and all opioid analgesics were expressed as the oral equivalent daily morphine use. According to the international consensus criteria [16], complete response was defined as a pain score of 0 without increase in analgesic use. Partial response was defined as pain reduction of at least 2 points without increase in analgesic use, or at least 25% reduction in opioid use without increase in pain score. Patients were classified as responders if a complete or partial response was achieved on at least one of the follow-up time points. All other patients were classified as non-responders. Patients who died within 2 weeks were regarded as patients with an unknown pain response. In case a patient did not return the BPI, a research nurse contacted the patient by phone or the patient's medical records were consulted for notes of the telephone contact with the doctor during follow-up. The date of return of the questionnaire or date of telephone contact, either by nurse or doctor, was recorded. For performance status, either WHO or KPS score was recorded. KPS scores were converted into WHO scores for uniform reporting [17]. Survival data were obtained through the population registry until 5 June 2017. For patients with multiple treatment fields, only lesions treated at baseline were taken into account. In cases where patients reported separate pain scores for separate lesions during follow-up by telephone contact, the highest pain score was recorded. Patients with a response for one lesion, but not for another were regarded non-responders.

Statistical analysis

Descriptive statistics were provided as percentages for proportions, mean and 95% confidence intervals (95% CI) or median and ranges for continuous values. Several proportions of response were calculated: the response rate in the total treated population, the response rate in the population surviving at least 2 weeks after treatment, and the response rate in the assessable population (*ie*, all patients who reported pain scores). In addition, three sensitivity analyses were performed. First, a worst case scenario analysis, assuming all patients without information on pain response to be a non-responder. In a second analysis, patients without information on pain response were assumed responders. Finally, to explore the influence of the time frame on the pain response rate, pain response was calculated between 4 and 8 weeks following radiotherapy. Pain response rates were assessed for three subgroups: in patients with breast or prostate cancer, in patients with spinal metastases, and in patients in good physical condition (*ie*, WHO status 0–1). Time to response was measured from date of treatment to date of first response. Survival was measured from date of radiation treatment to date of death or last contact. Response duration was calculated in days in patients who experienced pain relief from the first evaluable date of response to the date of relapse (defined as an increase in pain or analgesic use score as compared to baseline), or in absence of relapse to the date of last assessment or death. Retreatment was considered relapse. To measure percentage of remaining time spent with pain relief, the net pain relief (NPR) was calculated by dividing the period of pain relief by the period of survival in days and multiplying the result by 100 [16, 18]. All statistical analyses were performed using IBM SPSS statistics version 23.0 (IBM Corp., Armonk, NY, USA). We reported our results according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

RESULTS

Of all patients who were invited for the PRESENT study, 87% agreed to participate (Figure 1). Five-hundred patients were enrolled between June 2013 and August 2015. Of these, 432 patients were eligible for the present analysis. At baseline, 345 patients (80%) were treated for one painful lesion, 73 patients (17%) were treated for two lesions, 36 patients (2.5%) for three lesions, and two patients (0.5%) were treated for four lesions. The spine was the most affected site (64% of all treatment sites) (Table 1). Most common primary cancer sites were prostate (29%), breast (23%), and lung (23%). Sixty patients (14%) presented with pain and neurological complaints such as motor weakness or sensory deficits. During radiotherapy, 147 (34%) of the patients used corticosteroids for various reasons including neurological complaints, anti-tumor treatment, and prevention of pain flare.

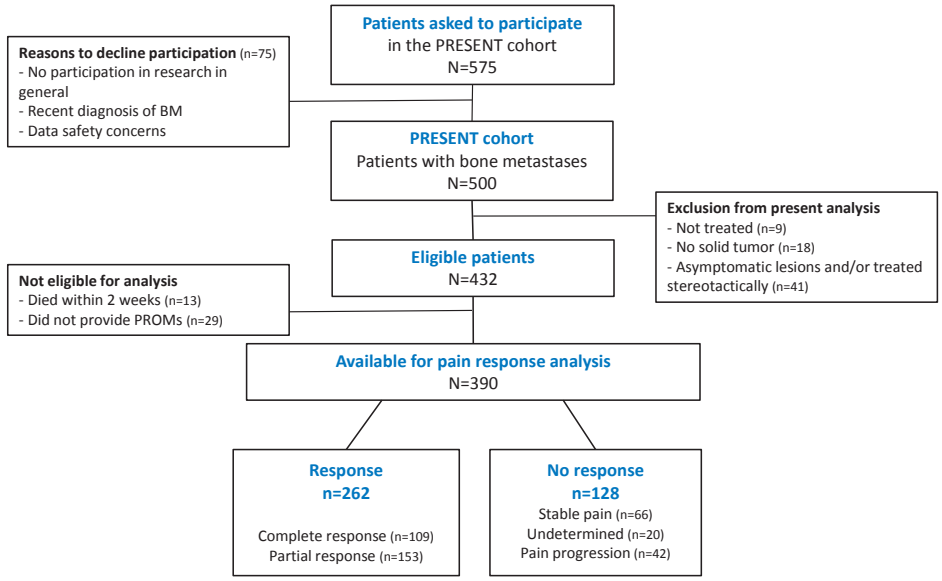

Figure 1. Study flow chart

Table 1. Characteristics of the first 500 patients in the PRESENT cohort

	Entire cohort N = 432	Non-assessable patients∞ N = 42
Gender		
Male	255 (59%)	27 (64%)
Female	177 (41%)	15 (36%)
Age		
Median (range)	67 (28–90)	64 (49–79)
Primary cancer site		
Prostate	127 (29%)	6 (14%)
Breast	97 (23%)	5 (12%)
Lung	97 (23%)	19 (45%)
Other	111 (25%)	12 (29%)
Localization‡		
Spine	302 (63%)	40 (72%)
Pelvis	98 (20%)	11 (20%)
Long bones	33 (7%)	1 (2%)
Ribs	12 (3%)	1 (2%)
Other	35 (7%)	2 (4%)

Table 1. Characteristics of the first 500 patients in the PRESENT cohort (*continued*)

	Entire cohort N = 432	Non-assessable patients∞ N = 42
Radiation treatment		
8 Gy; 1 x 8 Gy	290 (67%)	50 (86%)
30 Gy; 10 x 3 Gy	72 (17%)	3 (5%)
Other	70 (16%)	5 (9%)
Visceral and/or brain metastases		
Yes	182 (42%)	24 (57%)
Missing	*14 (3%)*	*1 (2%)*
WHO performance status*		
WHO 0–1	202 (53%)	9 (36%)
WHO 2	146 (39%)	19 (76%)
WHO 3–4	32 (8%)	7 (28%)
Pain score		
Mean ± SD	6.4 ± 2.2	6.5 ± 2.6
Median (range)	7 (0–10)	6.5 (0–10)
Pain medication†		
No use	36 (8%)	0
Phase 1 or 2	130 (30%)	7 (17%)
Phase 3 or 4	264 (62%)	34 (81%)
Use of corticosteroids‡		
No	269 (62%)	21 (50%)
Yes, during radiotherapy	18 (4%)	3 (7%)
Yes, for neurological complaints	29 (7%)	2 (5%)
Yes, for other reasons	53 (12%)	11 (26%)
Yes, for unknown reasons	47 (11%)	4 (10%)

∞Patients not returning questionnaires during follow-up
‡In total, 73 patients had two or more lesions at baseline
*The WHO is a conditional score ranging from 0 (normal situation, no complaints) to 4 (completely disabled). Of 52 patients (12%), WHO status was missing.
† Pain medication phase 1: non-opioids like paracetamol, NSAIDs, phase 2: mild opioids like tramadol, phase 3: strong opioids like morphine, phase 4: non-oral administration of opioids. Data on pain medication was missing in 2 patients (0.004%).
** Using students t-test, chi-square test, or ANOVA analysis comparing assessable patients (n=390) with non-assessable patients
‡For corticosteroid use, data of 16 patients (4%) were missing.

During a median follow-up of three months, 89 patients (21%) developed new painful lesions outside the initial radiation target volume, which were subsequently irradiated. Median time to irradiation of these new lesions was 17 weeks (range 2–80 weeks). Of these 89 patients, 36 patients (40%) developed new painful lesions within 12 weeks after irradiation of the baseline lesion. Twenty patients (55%) experienced a response before they were treated for a new lesion, 5 patients (14%) had not experienced a response before they were treated for a new lesion, 9 patients (25%) had progressive disease only or died within 12 weeks.

Table 2. Best response outcomes in 2–12 weeks after radiotherapy according to consensus criteria [16]

Response type	Total treated population (n=432)	All patients surviving at least 2 weeks patients (n=419)	Assessable patients (n=390)	Worst case scenario (n=432)	Best case scenario (n=432)
Responders	262 (61%)	262 (63%)	262 (67%)	262 (61%)	304 (70%)
Complete response	*109 (25%)*	*109 (26%)*	*109 (30%)*	*109 (25%)*	*NA*
Partial response	*153 (36%)*	*153 (36%)*	*153 (38%)*	*153 (36%)*	*NA*
Non-responders	128 (29%)	128 (30%)	128 (33%)	170 (39%)	128 (30%)
Stable pain	*66 (16%)*	*66 (16%)*	*66 (17%)*	*NA*	*NA*
*Undetermined**	*20 (5%)*	*20 (5%)*	*20 (5%)*	*NA*	*NA*
Pain progression	*42 (10%)*	*42 (10%)*	*42 (10%)*	*NA*	*NA*
Unknown	42 (10%)	29 (7%)	NA	NA	NA

*Response not captured by response, stable pain or pain progression, for example a patient with decreasing pain scores with simultaneously increasing opioid use

The 42 patients who did not return the pain questionnaires were different from the rest of the cohort participants: they had more often lung cancer as a primary tumor, were more often treated with single fraction radiation therapy, and their physical condition was worse compared with patients who returned the questionnaires (Table 1).

Pain response

Response rates of 390 patients (90%) were available (Table 2). Response rates were based on returned questionnaires (71%) or follow-up phone call (29%). In the total treated population, 262 patients experienced a response (61%, 95% CI 56–65%). Patients treated with long course radiotherapy experienced pain relief more often compared to patients treated with 8 Gy in a single fraction (72 *vs.* 55% respectively, p=0.001). The response rate in the population surviving at least 2 weeks after treatment was 63% (95% CI 58–67%). Of all assessable patients (*ie,* all patients excluding those who did not provide pain scores or who died within 2 weeks) the response rate was 67% (95% CI 62–72%). In the worst-case scenario analysis, the proportion of response was 61% (*ie,* the proportion of responders in the total study population). In the scenario in which patients with an unknown response were regarded responders, the response rate was 70% (95% CI 66–75%). Finally, the period in which pain response rate was recorded was of influence of the response rate. The response rates between week 4 and week 8 was 51% (95% CI 46–56%) for the total treated population (worst case scenario), and 62% (95% CI 57–67%) for the assessable patients (Table 3). Median time to response was 4 weeks (range 1–15 weeks). When patients experienced pain relief, the median duration of pain response was 21 weeks (range 0–190 weeks). The NPR in this population was 64% (95% CI 60–66%), indicating that responding patients spent around two-third of their remaining life experiencing a relief of their pain.

Table 3. Best response outcome in 2–12 weeks after radiotherapy, per subgroup

Response type	Total treated population (n= 432)	Patients <68 years (n=234)	All patients with breast or prostate cancer (n=224)	All patients with spinal metastases (n=289)†	Patients in good physical condition** (n=202)
Responders	262 (61%)	132 (56%)	157 (70%)	172 (60%)	140 (70%)
Complete response	*109 (25%)*	*49 (21%)*	*71 (32%)*	*72 (25%)*	*67 (33%)*
Partial response	*153 (35%)*	*83 (36%)*	*86 (38%)*	*100 (35%)*	*73 (36%)*
Non-responders	128 (27%)	78 (33%)	56 (25%)	85 (29%)	53 (26%)
Stable pain	*66 (16%)*	*42 (18%)*	*29 (13%)*	*47 (16%)*	*27 (13%)*
Undetermined	*20 (5%)*	*9 (4%)*	*7 (3%)*	*15 (5%)*	*8 (4%)*
Pain progression	*42 (10%)*	*27 (11%)*	*20 (9%)*	*23 (8%)*	*18 (9%)*
Unknown	42 (10%)	24 (11%)	11 (5%)	32 (11%)	9 (4%)

*All patients younger than 68 year
†Number of patients is lower than number of spinal lesions: some patients had more than one spinal lesion which needed radiation therapy
**All patients with WHO performance status of 0 or 1, indicating no or few symptoms

Subgroup analyses

Of all patients with spinal metastases, 60% (95% CI 54%–65%) of the patients experienced a pain response. Patients with breast or prostate cancer (n=224) and patients in good physical condition (n=202) had higher response rates of 70% (95% CI 64%–76%) and 69% (95% CI 63%–76%) respectively. For the entire cohort and all subgroups, pain scores were lowest at 6 weeks after radiotherapy, after which mean pain scores increased again but were still lower compared to baseline (Figure 2).

Survival analyses

Median time between diagnosis of the primary tumor and diagnosis of first bone metastases was 8 months (range 0–468 months). Between diagnosis of first bone metastases and initiation of radiation therapy, the median time elapsed was 3 months (range 0 – 169 months). Thirteen patients (3%) died within two weeks after radiation treatment, and 117 patients (27%) died within three months. One year post-treatment 260 patients (60%) had died. For the entire cohort, median survival was 8 months (range 0–46 months). The median survival between patients with and patients without a pain response differed significantly (13 *vs.* 5 months respectively, $p<0.001$).

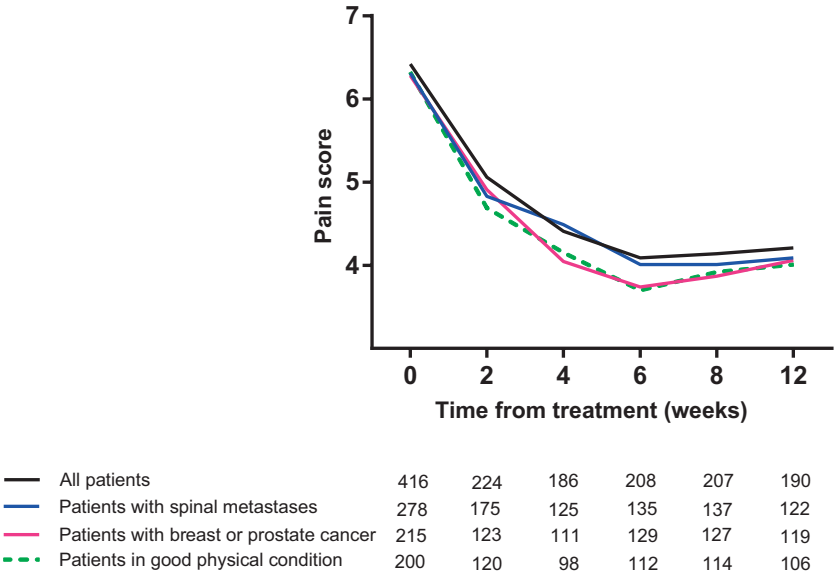

Figure 2. Pain scores during the first 3 months after treatment for all patients, patients with spinal metastases, patients with breast or prostate cancer, and patients in good clinical condition (*ie, WHO score 0–1).* Pain was scored on an 11-point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). The numbers below the graph indicate the number of patients that provided pain scores at specific time points.

DISCUSSION

In our prospective PRESENT cohort, pain response rates were 61% in the total treated population and 67% in the assessable patients. Given the median time to response, it is important to inform patients that pain response may still occur after 4 weeks. In line with the literature, pain response for patients with spinal metastases was comparable to pain response in the entire cohort [20–22] and the best responders were patients with metastases from breast or prostate cancer, and patients in good physical condition [23]. As long course radiotherapy is, in our department, reserved for patients in a (relatively) good physical condition with bone metastases from (relatively) favorable tumors, it was not surprising that significantly more patients experienced pain relief after long course radiotherapy.

The pattern of pain response in this unselected cohort of patients with bone metastases is comparable with response rates reported in randomized trials over the past decades. The pooled estimate of the response rates from 25 randomized controlled trials is approximately 60% [3, 4]. Of these randomized controlled trials, only two randomized trials adhered to the international consensus guidelines for reporting outcomes [23, 24]. Pain response rates from these two trials

were slightly higher compared to pain response in the current PRESENT cohort. Looking at the intention-to-treat population in the Dutch Bone Metastases Study, an overall response rate of 68–69% in more than 1100 patients recruited in 17 Dutch hospitals was found [25]. Foro Arnalot *et al.* found response rates of 76–87% in a study population of 160 patients [24]. In this trial, patients with more than one painful site, and patients with spinal cord compression were excluded, as were patients who received prior radiotherapy or patients in an overall poor state of health. Potentially, these patients have more often progressive disease and are therefore less likely to respond to radiotherapy [2, 26]. This patient category was included in the PRESENT cohort, which may help explain the somewhat lower response rate in the current study. Another factor that could have contributed to some extend to the lower rate is the introduction of stereotactic radiotherapy in our department in November 2014. Patients eligible for stereotactic radiotherapy are recruited in the PRESENT cohort, but were excluded from the current analysis. Almost 80% of the patients in our department who underwent stereotactic radiotherapy had oligometastatic disease and more than 80% had a WHO performance status of 0 or 1. In contrast, only 53% the patients in the cohort under study had a WHO performance status of 0 or 1. As stereotactically treated patients represent a healthier subgroup, their expected response rates are higher [2, 26]. Hypothetically adding these patients to this analysis, assuming these patients would all respond to radiotherapy, the response rate would have been near 70%.

The Dutch Bone Metastases Study is considered a landmark project since it is one of the largest studies assessing the response of patients with painful bone metastases after palliative radiotherapy [23, 25]. In this study, patients who needed treatment of more than one lesion were excluded, as were patients who were irradiated previously, had spinal cord compression, or metastases in the cervical spine. Patients with metastases from malignant melanoma or renal cell carcinoma were also excluded. Patients with these characteristics (36 patients, 8% of the entire cohort) were included in the PRESENT cohort, and may explain the somewhat lower response rates. Furthermore, up to 3 months pain response of the patients in the Dutch Bone Metastases Study were measured every week. Patients in the PRESENT cohort are asked to fill out questionnaires every other week, thereby increasing the chance of not recording an perceived pain response.

For PRESENT we systematically approach all patients with bone metastases inviting them to participate. Patients are followed prospectively with extensive measures including patient-reported outcomes and clinical data for a long(er) period of time. Lost-to-follow-up rates are very low in PRESENT (10%) compared to cohorts from other hospitals (19–78%) [7, 22, 27]. Response rates after palliative radiotherapy for bone metastases very much depend on how outcome is reported, with substantial differences between response rates based on the total treated population and those calculated in assessable patients. In addition, the follow-up period in which response is measured is of major influence with a difference in response rate of 10% between the shorter and longer follow-up periods. Due to the natural course of the disease, lost-to-follow-up

is very common in this study population. Patients are often admitted to the hospital or deteriorate at home, the result of which hampers the return of questionnaires leading to missing data. These missing outcomes are not likely missing at random, and simply removing patients who are lost to follow-up will most likely overestimate the proportion of patients who experience a pain response. Accordingly, researchers should report both the response rates of their total treated population and the results of assessable patients to show the effects of this potential bias.

In 2012, the international consensus guideline was updated to include the NPR in addition to other assessments of pain response. In the PRESENT cohort, the NPR is 64% indicating that responsive patients spent around two-third of their remaining life with less pain, without the need for retreatment. Probably, this is an underestimation as there are PRESENT patients who are still alive without reported pain recurrence. It is important to realize that in the last weeks before death, pain intensifies in patients with bone metastases, which has a negative impact on quality of life [28]. Although the use of the NPR is recommended for several years now, this measure is rarely reported. Only the group of Foro Arnalot *et al.* reported the NPR, which was slightly higher compared to the NPR we have found (68%–71%) [24]. In the DBMS, NPR was 70% (data not published). As the NPR includes the period of pain relief, one might argue that this outcome measure is more relevant to patients than the binary statement of response. Indeed, patients with a short period of relief do count as responders but contribute little time to the (numerator of the) NPR making this more relevant to patients.

Follow-up in our cohort included data on pain scores and analgesic use, allowing us to report our outcomes according to the international consensus guidelines [16]. However, the recommendation is to only account for opioid use when calculating response rates. In our cohort, we found that more than 30% of patients used corticosteroids during radiotherapy. Corticosteroids could also have a beneficial effect on relieving pain [29]. Furthermore, patients also use tricyclic antidepressants or antiepileptic drugs for neuropathic pain. When calculating response rates, changes in the use of corticosteroids, tricyclic antidepressants or antiepileptic drugs were not taken into account. In line with the consensus guidelines, patients with 25% decreased opioid use were counted as responders in our analyses. It is possible that patients using corticosteroids or neuropathic pain medication also had reduced intake of these analgesics as result of response after radiotherapy, but were not regarded as responders.

We acknowledge this study has some limitations. As radiotherapy is a local treatment, ideally the response to just the index lesion is measured. However, it is difficult for patients with multiple lesions to distinguish between painful lesions at relatively small distances and give separate pain scores. As we asked patients to indicate their worst pain score, it might be that radiotherapy was successful for one lesion, but not for another. In fact, treatment to the index lesion might have *unmasked* other lesions appearing more symptomatic. Furthermore, taking analgesic use

into account when calculating response is challenging if analgesic doses are increased when other metastatic lesions become (more) symptomatic. In the PRESENT cohort, we enroll all patients with bone metastases, including those patients with multiple painful lesions, possibly lowering the pain response rate. However, the majority of the PRESENT patients (80%) had bone metastases treatable in one target volume. Another limitation might be our time frame of response, since we calculated response up to 3 months after radiotherapy. It might be that patients who did not experience pain relief from radiotherapy started with systemic anticancer treatments, such as chemotherapy, hormonal therapy, or radiopharmaceuticals. These systemic treatments could have induced a pain response which was (mistakenly) attributed to radiotherapy and pain response might thus be overestimated. However, as some patients might experience a response even after 12 weeks [30], we decided to include all responses up to 12 weeks. Finally, we included patients with neurological complaints as well. Their origin of pain and their response to radiotherapy might be different from patients without neurological complaints [31].

In conclusion, in our cohort the majority of patients with painful bone metastases treated with palliative radiotherapy experienced pain relief. However, a large portion of patients did not respond to radiotherapy. New interventions or combination of conventional treatments for patients with symptomatic bone metastases should aim at improving pain relief. Before implementation in routine clinical care, these interventions are ideally all evaluated in randomized trials. The PRESENT cohort, conducted according to the cmRCT design provides an infrastructure aiming at more efficient evaluation of new (combinations of) treatments. Furthermore, it is important to identify the patients who are not likely to respond as they might benefit more from early and proactive palliative care management.

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CHAPTER 3

Development and internal validation of a clinical risk score to predict pain response after palliative radiation therapy in patients with bone metastases

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SUMMARY

Radiation therapy is effective in reducing pain in approximately 60% of patients with bone metastases. We developed a prediction model to help identify patients who are unlikely to respond to palliative radiation therapy. Primary tumor site, performance status, and baseline pain score were associated with pain response and were modestly able to discriminate good and poor responders.

ABSTRACT

Purpose

To investigate the relationship between patient and tumor characteristics and pain response in patients with metastatic bone disease, and construct and internally validate a clinical prediction model for pain response to guide individualized treatment decision making.

Material and Methods

A total of 965 patients with painful bone metastases undergoing palliative radiation therapy at a tertiary referral center between 1999 and 2007 were identified. Pain scores were measured at 1, 2, and 3 months after radiation therapy. Pain response was defined as at least a 2-point decrease on a pain score scale of 0-10, without increase in analgesics, or an analgesic decrease of at least 25% without an increase in pain score. Thirteen candidate predictors were identified from the literature and expert experience. After multiple imputation, final predictors were selected using stepwise regression and collapsed into a prediction model. Model performance was evaluated by calibration and discrimination and corrected for optimism.

Results

Overall 462 patients (47.9%) showed a response. Primary tumor site, performance status, and baseline pain score were predictive for pain response, with a corrected *c*-statistic of 0.63. The predicted response rates after radiation therapy increased from 37.5% for patients with the highest risk score to 79.8% for patients with the lowest risk score and were in good agreement with the observed response rates.

Conclusions

A prediction score for pain response after palliative radiation therapy was developed. The model performance was moderate, showing that prediction of pain response is difficult. New biomarkers and predictors may lead to improved identification of the large group of patients who are unlikely to respond and who may benefit from other or innovative treatment options.

INTRODUCTION

Many patients with cancer will develop symptomatic metastatic bone disease at some point during their lives, and up to 70% of terminal cancer patients have bone metastases [1]. Pain is a common consequence of bone metastases, which strongly interferes with quality of life and daily functioning [2]. Survival of patients with bone metastases varies greatly and ranges from a few months in patients with multiple organs involved to several years for patients with skeletal metastases exclusively [3]. With the advent of increasingly effective systemic treatment the prognosis of patients with bone metastases has improved. With these improving survival rates, maintaining the quality of a patient's remaining life is becoming more important. Radiation treatment, the standard local treatment for patients with painful bone metastases [4], is a patient-friendly and cost-effective intervention. Meta-analyses of radiation therapy trials have consistently shown a pain relief rate of approximately 60% [5-7], implying that up to 40% of patients do not adequately benefit from standard radiation therapy. Accurate prediction of patients who are unlikely to respond to radiation treatment is necessary to identify patients who might benefit more from other treatments, such as switching analgesic regimen, (radio)surgery, or systemic therapy. Additionally, better insight into the association between clinical determinants and poor response might help guide researchers in the development of innovative treatments as an alternative or addition to standard (radiation) treatment. Several factors have been shown to affect pain response, including primary tumor site, performance status, and location of the metastases [8-11]. In the present study we aimed to investigate the relationship between patient and tumor characteristics and pain response in patients with metastatic bone disease, and construct and internally validate a clinical prediction model for pain response to guide individualized treatment decision making.

METHODS AND MATERIAL

This study follows the reporting guidelines of the TRIPOD statement [12].

Patient selection

The Rapid Response Radiotherapy Program (RRRP) at the Sunnybrook Odette Cancer Centre, a tertiary referral center, is a program that provides palliative radiation to outpatients with advanced cancer. Bone metastases are present in approximately 70% of patients. We pooled prospectively collected data of consecutive enrolled patients with bone metastases who attended the RRRP clinic between January 1999 and December 2007. These data have been reported previously with alternative study aims [13, 14]. For these studies ethics approval was obtained from the Sunnybrook Health Science Centre research ethics board.

Assessment of the outcome

In accordance with the international consensus criteria [15], pain response was defined as a decrease in initial worst pain score by at least 2 points at the irradiated site, without increase in analgesic use, or an analgesic decrease of at least 25% without an increase in pain score. Response to radiation therapy was measured at 1, 2, and 3 months after radiation therapy. In case an outcome was not recorded in the original study databases, hospital charts were consulted. Patients were categorized as responders if they met the criteria for pain response on at least 1 of the follow-up time points; those who did not show pain response were regarded nonresponders. Patients who died within 4 weeks after radiation therapy (*ie*, before the first assessment of response) were considered nonresponders.

Selection of clinical determinants

Selection of determinants of pain response was based on the literature and clinical experience and included primary tumor site (breast and prostate, lung, or other), interval between diagnosis of primary tumor and diagnosis of first bone metastasis (dichotomized as within 1 year, *vs.* after at least 1 year), Karnofsky performance status (40, 50-70, and ≥80), gender, age (continuous), dose (8 Gy in 1 fraction, or other), localization of metastatic bone pain (spine, pelvis, ribs, long bones, or other), radiation therapy preceded by surgery (yes or no), presence of visceral metastases at time of radiation therapy (yes or no; if no test were performed it was considered as no visceral metastases), presence of positive lymph nodes at time of radiation therapy (yes or no), previous systemic treatment (yes or no), pain score (continuous), and use of opioid pain medication (categorized as no morphine use, low morphine use [<35 mg], medium morphine use [36-120 mg], and high morphine use [≥121 mg]).

Statistical analysis

On the basis of the numbers of events (*ie*, treatment failures), at least 30 predictive parameters were allowed to be selected for response prediction following the 1-in-10 rule [16]. Continuous variables were presented as mean ± standard deviation when normally distributed and as median (range) in case of a skewed distribution. Categorical data were presented as frequencies with percentages. To compare the categorical and continuous variables at baseline, χ^2 tests and Mann-Whitney tests were used. Missing data were considered missing at random and were imputed 20 times. The multiple imputation procedure was performed with all predictors in the imputation process, including the outcome. The default for imputation was taken in R for each variable: predictive mean matching for continuous data, logistic regression for binary data, and proportional odds for ordered categorical data. A logistic regression model was developed in a complete dataset to obtain odds radios for response with 95% confidence intervals for the selected parameters. In this model, all continuous variables were retained on the original scale. An interaction term was created between worst pain at baseline and the use of opioid pain medication because the amount of opioid pain medication might depend on the pain score. Starting

with a full prediction model that included all candidate predictors and the interaction, variables were selected with a backward stepwise approach [17]. In each step the least significant variable was excluded based on Akaike's information criterion. The concordance statistic (*c*-statistic), which is equivalent to the area under the receiver operating characteristic curve, was used to assess the model's discriminative ability [18]. To correct for optimism, internal validation of the model was performed using 2000 bootstrap resamples of the original dataset, in which all modeling steps were repeated. These steps were done for all 20 imputed datasets. The performance of the final models of the 20 imputed datasets was pooled and used to calculate the optimism of the original model. Subsequently, the coefficients (βs) from the original model were adjusted by the shrinkage factor obtained by bootstrapping. The *c*-statistic was calculated for all 20 imputed datasets and subsequently averaged to retrieve the corrected value and its range. The optimism-corrected βs were used in further analyses (*ie*, calibration and risk score creation). In addition to the main analysis (*ie*, inclusion of all patients in the analysis with missing data imputed), we performed sensitivity analyses: a complete case analysis, a "best case scenario" analysis, a "worst case scenario" analysis, an analysis in which the patients who died within 4 weeks after radiation therapy were excluded, and an analysis in which the outcomes were imputed for the patients who died within 4 weeks after radiation therapy. For the complete case analysis, only those patients with a known outcome were included. In the best case scenario analysis, a best possible overall response rate was calculated assuming all patients without a recorded outcome were responders. In the worst case scenario analysis, a worst case overall response rate was calculated assuming that all patients without a recorded outcome were nonresponders. For the sensitivity analysis, missing data in predictors were imputed using the same method as described for the main analysis. SPSS software version 23.0 (IBM, Armonk, NY) and the R language environment (version 3.2.1; R Foundation for Statistical Computing, Vienna) were used for all statistical analyses [19]. Multiple imputation was performed using the mice package [20]. The rms package was used for model construction, internal validation, and calibration of the final model [21]. The R script is available upon request.

Risk score construction

The final model was presented as a risk score. The contribution of each predictor to the risk score was transformed into a score by multiplying the optimism-corrected coefficients by 10 and rounding these to 0.1 precision. For every patient an individual risk score was calculated by multiplying the contribution of the variables to the risk score by the value of the variables themselves and adding them up. This score was subsequently divided into risk groups in such a way that for every group the difference in predicted probability of response was at least 10% [12].

RESULTS

A total of 1027 patients with bone metastases who attended the RRRP clinic were included. Thirty-one patients were excluded because these patients did not undergo palliative radiation therapy. Patients with baseline scores of 0 or 1 without analgesic use were excluded (n=31), leaving 965 patients for analysis. The majority of patients were male (57%), and the median age of the study cohort was 68 (range, 28-95) years (Table 1). Most common primary tumor sites included breast, prostate, or lung (26%, 24%, and 25%, respectively). The most common location for metastases was the spine (37%). A total of 462 patients (48%) experienced a response within 3 months after palliative radiation therapy; 311 patients (32%) did not experience a response, including 88 patients who died within 4 weeks after radiation therapy. One hundred ninety-two patients (20%) had no follow-up data. With regard to missing data, 134 patients (14%) had no missing values, and the majority of patients had 1 missing value (40%). Data were not missing completely at random (Table E1). Multivariable analysis showed that primary tumor site, Karnofsky performance status, and baseline pain scores were the strongest predictors of pain

Table 1. Patient characteristics of patients with and without response to radiation therapy

	Response to RT	No response to RT	Response Unknown	p-value*
Characteristic	N = 462	N = 311	N = 192	
Gender				
Female	205 (44%)	121 (40%)	86 (45%)	
Male	257 (56%)	190 (61%)	106 (55%)	0.08
Age (median, range)	67 (31–95)	68 (28–94)	69 (31–89)	0.72
Primary cancer site				
Breast or prostate	282 (61%)	127 (41%)	72 (38%)	
Lung	97 (21%)	88 (28%)	58 (30%)	
Other	83 (18%)	96 (31%)	62 (32%)	<0.001
Period between diagnosis primary tumor and bone metastases				
Less than 1 year	122 (26%)	88 (28%)	40 (21%)	
More than 1 year	139 (30%)	58 (19%)	34 (18%)	0.01
Missing	*201 (44%)*	*165 (53%)*	*118 (61%)*	
Karnofsky performance status†				
80–100	150 (33%)	60 (19%)	35 (18%)	
50–70	273 (59%)	204 (66%)	124 (65%)	
20–40	25 (5%)	35 (11%)	24 (12%)	<0.001
Missing	*14 (3%)*	*12 (4%)*	*9 (5%)*	
Radiation treatment schedule				
8 Gy; 1 x 8 Gy	233 (50%)	149 (48%)	105 (54%)	
Other	228 (49%)	161 (52%)	84 (44%)	0.51
Missing	*1 (1%)*	*1 (1%)*	*3 (2%)*	

Table 1. Patient characteristics of patients with and without response to radiation therapy (*continued*)

	Response to RT	No response to RT	Response Unknown	p-value*
Characteristic	N = 462	N = 311	N = 192	
Localization				
Spine	169 (37%)	123 (39%)	63 (33%)	
Pelvis	160 (35%)	99 (32%)	58 (30%)	
Long bones	65 (14%)	43 (14%)	26 (14%)	
Ribs	24 (5%)	19 (6%)	21 (11%)	
Other	44 (9%)	27 (9%)	24 (12%)	0.86
Post-operative radiotherapy				
Yes	6 (1%)	9 (3%)	11 (6%)	
No	456 (99%)	302 (97%)	181 (94%)	0.18
Visceral and/or brain metastases				
Present	176 (38%)	117 (38%)	65 (34%)	
No	193 (42%	132 (42%)	79 (41%)	0.87
Missing	*93 (20%)*	*62 (20%)*	*48 (25%)*	
Lymph nodes metastases				
Present	92 (20%)	64 (21%)	42 (22%)	
No	144 (31%)	117 (37%)	69 (36%)	0.48
Missing	*226 (49%)*	*130 (42%)*	*81 (42%)*	
Previous systemic treatment				
Yes	272 (59%)	155 (50%)	86 (45%)	
No	98 (21%)	103 (33%)	63 (33%)	<0.001
Missing	*92 (20%)*	*53 (17%)*	*43 (22%)*	
Baseline pain score				
Mean ± SD	6.7 (±2.5)	6.3 (±2.7)	6.6 (±2.5)	0.30
Missing	*1 (1%)*	*3 (1%)*	*1 (1%)*	
Use of opioid pain medication				
None	121 (26%)	63 (20%)	65 (34%)	
Low (1–35 mg)	112 (24%)	69 (22%)	26 (13%)	
Medium (36–120 mg)	101 (22%)	73 (24%)	40 (21%)	
High (>120 mg)	98 (22%)	91 (29%)	52 (27%)	0.04
Missing	*27 (6%)*	*15 (5%)*	*9 (5%)*	

Abbreviations: Gy = gray; RT = radiotherapy; SD = standard deviation
*Chi-Square test or t-test comparing patients having a response after radiotherapy with patients without a response
†The KPS is a conditional score ranging from 0% (death) to 100% (normal situation, no complaints)

response (Table 2). These predictors were confirmed by the 5 sensitivity analyses (Tables E2-E6). The regression coefficients in the final model were multiplied with the estimated shrinkage factor of 0.88 to obtain optimism-corrected odds ratios (Table 2). In the risk score, divided into 5 risk groups, the predicted response rates after radiation therapy increased from 37.5% to 79.8% with decreasing score categories and were in good agreement with the observed response rates (Table 3). The apparent *c*-statistic was 0.66 (range, 0.62-0.69) indicating a reasonable discriminative ability in predicting pain response. After correction for optimism the *c*-statistic was 0.63. For the scenario analysis in which the patients who died within 4 weeks were excluded, the *c*-statistic was 0.59 (range, 0.55-0.62). Visual inspection of the consecutive model calibration plots showed a good overall fit (Figure 1).

Table 2. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases

	Univariable analysis		Multivariable analysis*		Contribution to risk score
Factor	OR (95% CI)	p-value	Corrected OR† (95% CI)	p-value	
Primary tumor					
Breast & prostate	1.00		1.00		0
Lung	0.48 (0.34-0.66)	<0.0001	0.50 (0.37-0.68)	<0.0001	7
Other	0.39 (0.27-0.56)	<0.0001	0.43 (0.31-0.60)	<0.0001	8
Interval Dx to first BM					
<1 year	1.00				
>1 year	1.51 (1.04-2.18)	0.029			
KPS					
80-100	1.00		1.00		0
50-70	0.53 (0.38-0.74)	0.0003	0.55 (0.41-0.75)	<0.0001	6
20-40	0.29 (0.17-0.51)	<0.0001	0.31 (0.19-0.52)	<0.0001	12
Sex					
Female	1.00				
Male	0.81 (0.62-1.06)	0.14			
Age	0.997 (0.985-1.009)	0.66			
Dose					
< 8 Gy	1.00				
>8 Gy	0.88 (0.67-1.14)	0.34			
Painful site					
Spine	1.00				
Pelvis	1.15 (0.82-1.61)	0.40			
Long bones	1.08 (0.70-1.68)	0.72			
Ribs	0.94 (0.51-1.76)	0.85			
Other	1.12 (0.67-1.88)	0.67			

Table 2. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases (*continued*)

	Univariable analysis		Multivariable analysis*		
Factor	OR (95% CI)	p-value	Corrected OR† (95% CI)	p-value	Contribution to risk score
Postoperative RT					
No	1.00				
Yes	0.42 (0.17-1.02)	0.06			
Visceral metastases					
No (tests)	1.00				
Yes	1.06 (0.74-1.51)	0.76			
Lymph nodes					
No (tests)	1.00				
Yes	1.21 (0.88-1.67)	0.24			
Previous systemic therapy					
No	1.00				
Yes	1.82 (1.34-2.47)	<0.0001			
Pain at baseline	1.06 (1.002-1.12)	0.04	1.08 (1.02-1.13)	0.007	0.7
Total morphine at baseline					
None	1.00				
Low	0.88 (0.58-1.31)	0.51			
Medium	0.69 (0.46-1.04)	0.07			
High	0.56 (0.37-0.83)	0.004			
Interaction					
Pain*none morphine	1.0				
Pain*low morphine	1.01 (0.86-1.19)	0.89			
Pain*medium morphine	1.08 (0.91-1.28)	0.39			
Pain*high morphine	1.11 (-0.95-1.30)	0.20			

Abbreviations: BM, bone metastases; CI, confidence interval; Dx, diagnosis; Gy, Gray; KPS, Karnofsky performance scale; OR, odds ratio; RT, radiotherapy
*Corrected model intercept is 0.679†Corrected for optimism by a shrinkage factor of 0.88

Table 3. Risk score for response after palliative radiotherapy according to score categories

Risk score*	n	Response	Predicted response (%)	Observed response (%)
<6	129	103	75.5%	79.8%
6 – 9	305	207	65.1%	67.9%
10 – 13	218	125	54.2%	57.3%
14 – 18	225	98	45.1%	43.6%
>19	88	33	35.1%	37.5%

*For calculation of risk score, see Table 2. For a patient with primary prostate carcinoma, KPS of 50–70 and a pain score at baseline of 6, the final tally of the risk score would yield 10.2 (*ie*, prostate carcinoma = 0 points; KPS 50-70 = 6 points; pain score of 6 = 6*0.7), indicating a predicted pain response of approximately 54%.

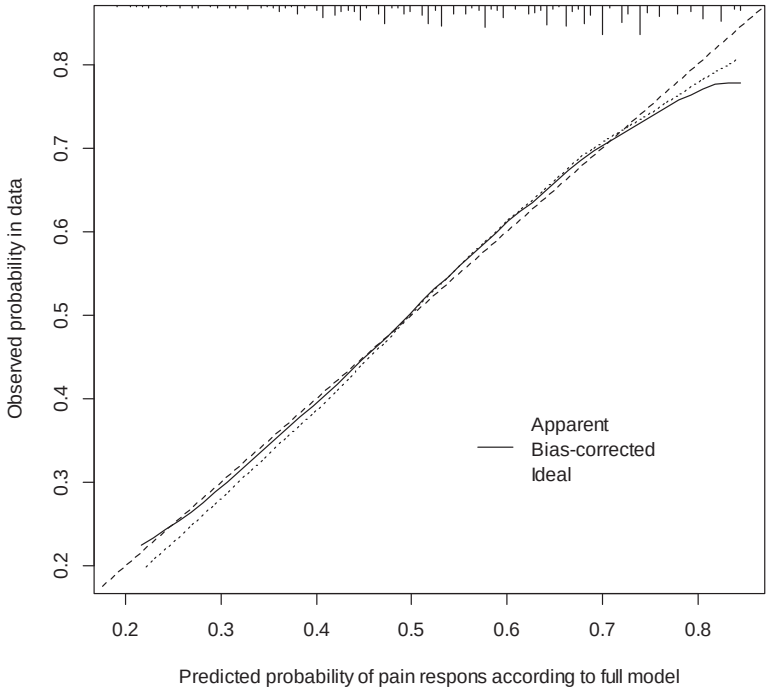

Figure 1. Calibration plot representing the observed *vs.* the predicted probability of pain response. The striped line is the optimal line for complete concordance between observed and predicted pain response. On the upper horizontal axis, the distribution of outcomes is depicted.

DISCUSSION

This study shows that pain response to radiation treatment can be predicted moderately well according to primary tumor site, Karnofsky performance status, and baseline pain score. Patients with breast or prostate cancer, high performance status, and high baseline pain scores have the highest probability of a pain response. Although the finding that patients with breast and prostate cancer have better pain response rates is consistent with the literature [9-11], there is no clear explanation why these patients respond better. Potentially, the standard radiation dose to metastatic sites is too high for fast-growing tumors (*eg*, small cell lung carcinomas), which may induce inflammation through early activation of cytokine cascades [22] and counteract the pain-killing effect of the radiation. Performance status is also a known predictor for pain response [8, 11], with patients having a low performance score responding less well to radiation therapy than patients with higher scores. Although the mechanism behind this phenomenon is unclear, it can be hypothesized that decreasing performance reflects progressive deterioration of physiologic and immunologic functions that may be necessary to elicit local (analgesic) effects after irradiation of the metastasis. Furthermore, patients in poor condition might experience pain originating from the (untreated) primary tumor or visceral metastases influencing their

overall pain score. Psychological phenomena may also play a role for patients failing to cope with the progressive nature of the disease, possibly leading to sensitization to pain for which radiation therapy might otherwise be effective. In this study a 1-point increase in baseline pain score increases the odds of radiation therapy success by 8%. It might be that there is more room for improvement in patients with high baseline pain scores. To qualify as a responder, a patient with a pain score of 4 needs a reduction of at least 50%, whereas a patient with a pain score of 8 needs a 25% reduction in pain score to qualify as a responder.

Other determinants of response have been studied previously, such as age, localization of painful lesion, number of treated lesions, dose, fractionation schedules, radiation treatment field size, soft-tissue extension, and imaging features [8-10, 23-28]. These studies had some limitations, including small sample sizes [23, 27, 28], retrospective collection of data on response (8), or absence of adjustment by multivariable modeling [8-10, 23-28]. To the best of our knowledge, only Westhoff *et al.* [11] constructed a multivariable prediction model. They used data from the Dutch Bone Metastases Study, a randomized controlled trial that compared single with multiple fractions for painful bone metastases in the late 1990s [29]. Here, primary tumor and performance status were predictive for response after radiation therapy. In addition, and in contrast to our results, the absence of visceral metastases and the use of opioid pain medication increased the chance of response, whereas baseline pain score (categorized at 2-4, 5-7, and 8-10) was not associated with response after radiation therapy. These differences might be attributed to the classification of patients for whom the presence of visceral metastases was unknown. With regard to use of opioid medication and baseline pain scores, some collinearity might be present, because opioids will be prescribed more to patients with high pain scores. After multivariable modeling 1 of the 2 factors is likely to be excluded. Despite the large sample size, the discriminative ability of the model of Westhoff et al was low, with a *c*-statistic, not corrected for optimism, of 0.56. Nonetheless, the results from both prediction models show that primary tumor, performance status, and a measure of the severity of pain patients experience at baseline are predictive for response after radiation therapy.

To improve the discriminative ability of the prediction model and accurately guide treatment decision making, adding new predictive variables beyond known clinical predictors might improve the prediction model. In this context, recent studies have shown promising results using imaging features of positron emission tomography [30-32] or serum and urinary markers of osteoclast activity [33-36]. The clinical relevance of these findings has not yet been validated. For monitoring of tumor response of bone metastases, conventional magnetic resonance imaging (MRI) is the most frequently used imaging modality [37]. Although several studies demonstrated the feasibility of using MRI to assess tumor response after conventional radiation therapy [38-40], only Switlyk *et al.*[41] evaluated the predictive value of MRI characteristics for pain response and did not find an association between pain response after conventional radiation therapy

and several imaging features. However, they did not include advanced MR techniques, such as diffusion-weighted MRI and dynamic contrast-enhanced MRI. Further research assessing biological imaging features from positron emission tomography and advanced MR techniques might provide additional predictive ability in the future. Finally, for spinal metastases, the degree of mechanical instability might be a predictive factor for pain response [42, 43].

In this study only half of the included patients experienced a response, leaving room for improvement of palliative radiation therapy. Nonresponding patients might benefit from other treatments, such as switching opioid regimes, radiopharmaceuticals, stereotactic radiation therapy, surgery, systemic therapy, or a combination of these options. All these treatments are already available but are less convenient for patients, associated with an increased risk of toxicity, or more expensive. To identify patients who are suitable candidates for other treatments than palliative radiation therapy, we need accurate discriminative and easy-to-use prediction models. Although the discriminative ability of the described prediction model and risk score is reasonable, our risk score is not discriminative enough for palliative radiation therapy to be omitted in certain patients, to offer those patients alternative treatments. Furthermore, the majority of patients do respond to palliative radiation therapy. Even patients with a high probability of being a nonresponder still have a 37.5% probability of response.

We acknowledge that there were some limitations to this study. The outcome was unknown in almost 20% of our patients, and these outcomes are likely missing either because the pain response is exceptionally good or because patients are unable to return the questionnaires because of progression of illness. However, it is most probable that these missing outcomes are – at least partly – related to earlier observed patient data, such as performance status and the presence of extra-osseous metastases. Thus, the probability that an outcome is missing depends on other observed patient characteristics. Therefore, a valid imputation model provided the proper imputation of missing data [44-46]. Second, because response status was only determined at 1, 2, and 3 months, the precise date of response was unknown. As a result, time to response could not be calculated, precluding competing risk analysis, which takes into account the fact that early death after radiation therapy is a competing risk for response. However, the aim of our risk score was to help physicians offer the optimal treatment to their patients. Therefore, patients who died within 4 weeks after radiation therapy were combined with nonresponding patients. Third, data from different studies were pooled for the present analysis. The study populations in these studies were, however, comparable because the aim of the different studies was to validate several questionnaires, and generally all patients attending the RRRP clinic were eligible for inclusion. Finally, although the results were internally validated by a bootstrapping technique, external validation of the risk score in an independent cohort of patients is required before clinical application of this score can be recommended.

In conclusion, primary tumor, performance status, and baseline pain score are associated with pain response in patients with bone metastases. Combining these factors into a risk score allows modest discrimination between patients who respond to radiation therapy and those who do not. Response rates after radiation therapy are suboptimal, and its prediction remains difficult, showing the need for new predictors in addition of development of innovative treatments for patients with painful bone metastases.

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APPENDICES

Table A1. Comparison of baseline characteristics of patients with completely observed data, 1 missing value, and >1 missing value*

Characteristic	No missing N = 131	1 missing N = 389	>1 missing N = 445	p-value**
Gender				
Female	59 (45%)	164 (42%)	189 (43%)	
Male	72 (55%)	225 (58%)	256 (58%)	0.840
Age (median, range)	67 (28–94)	68 (31–95)	68 (31–92)	0.553
Primary cancer site				
Breast or prostate	72 (55%)	210 (54%)	199 (45%)	
Lung	32 (24%)	95 (24%)	116 (26%)	
Other	27 (21%)	84 (22%)	130 (29%)	0.031
Period between diagnosis primary tumor and bone metastases				
Less than 1 year	65 (50%)	105 (27%)	80 (18%)	
More than 1 year	66 (50%)	107 (28%)	58 (13%)	
Missing	-	*177 (45%)*	*307 (32%)*	<0.001
Karnofsky performance status***				
80–100	28 (21%)	93 (24%)	124 (28%)	
50–75	91 (70%)	248 (64%)	262 (59%)	
20–40	12 (9%)	42 (11%)	30 (7%)	
Missing	-	*6 (1%)*	*29 (7%)*	<0.001
Radiation treatment schedule				
8 Gy; 1 x 8 Gy	62 (47%)	186 (48%)	239 (54%)	
Other	69 (53%)	203 (52%)	201 (45%)	
Missing	-	-	*5 (1%)*	0.039
Localization				
Spine	51 (39%)	150 (39%)	154 (35%)	
Pelvis	42 (32%)	110 (28%)	165 (37%)	
Long bones	22 (17%)	61 (16%)	51 (11%)	
Ribs	5 (4%)	29 (7%)	30 (7%)	
Other	11 (8%)	39 (10%)	45 (10%)	0.157
Post-operative radiotherapy Yes	2 (2%)	9 (2%)	15 (3%)	0.433
Visceral and/or brain metastases				
Present	57 (44%)	174 (44%)	127 (29%)	
Missing	-	*37 (10%)*	*166 (37%)*	<0.001

Table A1. Comparison of baseline characteristics of patients with completely observed data, 1 missing value, and >1 missing value* (*continued*)

	No missing	1 missing	>1 missing	
Characteristic	N = 131	N = 389	N = 445	p-value**
Lymph nodes metastases				
Present	59 (45%)	89 (23%)	50 (11%)	
Missing	-	*123 (32%)*	*314 (71%)*	<0.001
Previous systemic treatment				
Yes	88 (67%)	251 (65%)	174 (39%)	
Missing	-	*9 (3%)*	*179 (40%)*	<0.001
Baseline pain score				
Mean ± SD	6.3 (±2.7)	6.3 (±2.5)	6.8 (±2.5)	
Missing	-	*1 (0%)*	*4 (1%)*	0.005
Use of opioid pain medication				
None	33 (24%)	96 (25%)	122 (27%)	
Low (1–35 mg)	36 (27%)	97 (25%)	74 (17%)	
Medium (36–120 mg)	29 (22%)	96 (25%)	89 (20%)	
High (>120 mg)	35 (27%)	95 (24%)	111 (25%)	
Missing	-	*5 (1%)*	*49 (11%)*	<0.001
Treatment response				
Response	85 (65%)	205 (53%)	172 (38%)	
No response	46 (35%)	149 (38%)	116 (26%)	
Unknown	-	*35 (9%)*	*192 (20%)*	<0.001

*In total, 445 patients (46.1%) had >1 missing value, with 23.4% having 2 missing values, 14.3% having 3 missing values, 6.7% having 4 missing values, 1.6% having 5 missing values, and 0.1% having 6 missing values.
**Chi-Square test or t-test comparing patients having none missing values, 1 missing value, and >1 missing value
***The KPS is a conditional score ranging from 0% (death) to 100% (normal situation, no complaints)

Table A2. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases for the complete case scenario analysis

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Corrected OR* (95% CI)	p-value
Primary tumor				
Breast & prostate	1.00		1.00	
Lung	0.50 (0.35-0.71)	0.0001	0.47 (0.32-0.67)	<0.0001
Other	0.39 (0.27-0.56)	<0.0001	0.38 (0.26-0.55)	<0.0001
KPS				
80-100	1.00		1.00	
50-70	0.54 (0.38-0.77)	0.0006	0.50 (0.35-0.72)	0.0002
20-40	0.29 (0.16-0.53)	<0.0001	0.26 (0.14-0.49)	<0.0001
Pain at baseline	1.05 (1.00-1.11)	0.06	1.09 (1.02-1.15)	0.006

Table A3. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases for the worst case scenario analysis

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Corrected OR* (95% CI)	p-value
Primary tumor				
Breast & prostate	1.00		1.00	
Lung	0.47 (0.34-0.64)	<0.0001	0.45 (0.33-0.62)	<0.0001
Other	0.37 (0.27-0.51)	<0.0001	0.37 (0.26-0.51)	<0.0001
KPS				
80-100	1.00		1.00	
50-70	0.54 (0.40-0.73)	<0.0001	0.52 (0.38-0.72)	<0.0001
20-40	0.29 (0.17-0.49)	<0.0001	0.27 (0.15-0.46)	<0.0001
Pain at baseline	1.04 (0.99-1.09)	0.16	1.06 (1.01-1.12)	0.03

Table A4. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases for the best case scenario analysis

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Corrected OR* (95% CI)	p-value
Primary tumor				
Breast & prostate	1.00		1.00	
Lung	0.63 (0.45-0.88)	0.007	0.63 (0.45-0.88)	0.006
Other	0.54 (0.39-0.75)	0.0003	0.54 (0.39-0.75)	0.0003
KPS				
80-100	1.00		1.00	
50-70	0.65 (0.46-0.91)	0.01	0.63 (0.45-0.89)	0.009
20-40	0.47 (0.28-0.80)	0.005	0.45 (0.27-0.77)	0.003
Pain at baseline	1.05 (1.00-1.11)	0.05	1.07 (1.01-1.13)	0.02

Table A5. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases for the sensitivity analysis in which all patients who died within 4 weeks after radiotherapy were excluded

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Corrected OR* (95% CI)	p-value
Primary tumor				
Breast & prostate	1.00		1.00	
Lung	0.52 (0.35-0.75)	0.0007	0.51 (0.35-0.75)	0.0006
Other	0.45 (0.30-0.67)	0.0001	0.45 (0.30-0.67)	0.0001
Interval Dx to first BM				
<1 year	1.00			
>1 year	1.36 (0.92-2.02)	0.12		
KPS				
80-100	1.00		1.00	
50-70	0.67 (0.47-0.96)	0.03	0.64 (0.45-0.92)	0.01
20-40	0.59 (0.30-1.15)	0.12	0.53 (0.26-1.07)	0.08
Sex				
Female	1.00			
Male	0.80 (0.57-1.12)	0.19		
Age	1.00 (0.99-1.01)	0.83		
Dose				
< 8 Gy	1.00			
>8 Gy	0.90 (0.66-1.23)	0.52		
Painful site				
Spine	1.00			
Pelvis	1.07 (0.74-1.55)	0.72		
Long bones	1.28 (0.78-2.12)	0.33		
Ribs	0.88 (0.47-1.63)	0.67		
Other	1.06 (0.58-1.94)	0.84		
Postoperative RT				
No	1.00			
Yes	0.44 (0.15-1.33)	0.14		
Visceral metastases				
No (tests)	1.00			
Yes	1.03 (0.73-1.45)	0.86		
Lymph nodes				
No (tests)	1.00			
Yes	1.29 (0.86-1.94)	0.21		
Previous systemic therapy				
No	1.00			
Yes	1.65 (1.16-2.34)	0.006		
Pain at baseline	1.08 (1.01-1.15)	0.03	1.09 (1.02-1.17)	0.009
Total morphine at baseline				
None	1.00			
Low	0.98 (0.64-1.50)	0.94		
Medium	0.82 (0.53-1.26)	0.36		
High	0.83 (0.54-1.28)	0.40		
Interaction pain*morphine				
Pain*Low	1.01 (0.85-1.20)	0.92		
Pain*Medium	1.08 (0.90-1.29)	0.41		
Pain*High	1.11 (0.92-1.34)	0.27		

Table A6. Statistical analysis of factors predictive for pain response to radiotherapy for painful bone metastases for the sensitivity analysis in which the outcomes for all patients who died within 4 weeks after radiotherapy were imputed

Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	Corrected OR* (95% CI)	p-value
Primary tumor				
Breast & prostate	1.00		1.00	
Lung	0.55 (0.37-0.80)	0.002	0.54 (0.36-0.79)	0.002
Other	0.46 (0.32-0.66)	<0.0001	0.45 (0.31-0.65)	<0.0001
Interval Dx to first BM				
<1 year	1.00			
>1 year	1.36 (0.84-2.19)	0.20		
KPS				
80-100	1.00		1.00	
50-70	0.67 (0.48-0.94)	0.02	0.64 (0.45-0.91)	0.01
20-40	0.59 (0.31-1.10)	0.10	0.55 (0.29-1.05)	0.07
Sex				
Female	1.00			
Male	0.83 (0.61-1.22)	0.22		
Age	1.00 (0.99-1.01)	0.88		
Dose				
< 8 Gy	1.00			
>8 Gy	0.86 (0.64-1.14)	0.29		
Painful site				
Spine	1.00			
Pelvis	1.04 (0.73-1.48)	0.82		
Long bones	1.31 (0.80-2.15)	0.29		
Ribs	0.82 (0.44-1.53)	0.53		
Other	1.05 (0.61-1.83)	0.85		
Postoperative RT				
No	1.00			
Yes	0.40 (0.15-1.07)	0.07		
Visceral metastases				
No (tests)	1.00			
Yes	1.04 (0.75-1.43)	0.83		
Lymph nodes				
No (tests)	1.00			
Yes	1.27 (0.89-1.82)	0.19		
Previous systemic therapy				
No	1.00			
Yes	1.55 (1.06-2.27)	0.03		
Pain at baseline	1.08 (1.02-1.15)	0.006	1.10 (1.04-1.17)	0.001
Total morphine at baseline				
None	1.00			
Low	0.90 (0.59-1.39)	0.65		
Medium	0.80 (0.53-1.21)	0.29		
High	0.84 (0.55-1.26)	0.39		
Interaction pain*morphine				
Pain*Low	1.00 (0.83-1.19)	0.96		
Pain*Medium	1.09 (0.90-1.31)	0.38		
Pain*High	1.12 (0.93-1.34)	0.22		

CHAPTER 4

Prospective evaluation of the relationship between mechanical stability and response to palliative radiotherapy for symptomatic spinal metastases

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ABSTRACT

Background

A substantial number of patients with spinal metastases experience no treatment effect from palliative radiotherapy. Mechanical spinal instability, due to metastatic disease, could be associated with failed pain control following radiotherapy. This study investigates the relationship between the degree of spinal instability, as defined by the Spinal Instability Neoplastic Score (SINS), and response to radiotherapy in patients with symptomatic spinal metastases in a multi-institutional cohort.

Methods and Materials

The SINS of 155 patients with painful thoracic, lumbar, or lumbosacral metastases from two tertiary hospitals was calculated using images from radiotherapy planning CT scans. Patient-reported pain response, available for 124 patients, was prospectively assessed. Pain response was categorized, according to international guidelines, as complete, partial, indeterminate, or progression of pain. The association between SINS and pain response was estimated by multivariable logistic regression analysis, correcting for predetermined clinical variables.

Results

Of the 124 patients, 16 patients experienced a complete response and 65 patients experienced a partial response. Spinal Instability Neoplastic Score was associated with a complete pain response (adjusted odds-radio [ORadj] 0.78; 95% confidence interval [CI] 0.62–0.98), but not with an overall pain response (ORadj 0.94; 95% CI 0.81–1.10).

Conclusion

A lower SINS, indicating spinal stability, is associated with a complete pain response to radiotherapy. This supports the hypothesis that pain resulting from mechanical spinal instability responds less well to radiotherapy compared with pain from local tumor activity. No association could be determined between SINS and an overall pain response, which might indicate that this referral tool is not yet optimal for prediction of treatment outcome.

Implications for Practice

Patients with stable painful spinal metastases, as indicated by a SINS of 6 or lower, can effectively be treated with palliative external beam radiotherapy. The majority of patients with (impending) spinal instability, as indicated by a SINS score of 7 or higher, will achieve a (partial) response after palliative radiotherapy; however, some patients might require surgical intervention. Therefore, it is recommended to refer patients with a SINS score of 7 or higher to a spine surgeon to evaluate the need for surgical intervention.

INTRODUCTION

The incidence of patients with spinal metastases is increasing due to the increasing cancer incidence and the improved life expectancy of cancer patients [1–3]. Spinal metastases may cause debilitating pain and neurological deficits, impairing quality of life [4, 5]. Radiotherapy has been the standard of care for the treatment of uncomplicated painful spinal metastases. However, up to 70% of the patients treated with radiotherapy are resistant to treatment or experience only a partial response [6]. Surgery is offered to patients with mechanical spinal instability and patients with persisting or progressive neurological deficits. To ensure fast and effective symptom relief, optimal treatment selection is crucial considering the limited life expectancy of these patients. Previous studies have tried to identify predictive factors for response to palliative radiotherapy, but have shown inconsistent results [7–13]. Therefore, to optimize treatment and/or patient selection we need to identify new factors to predict treatment outcome. Pain from spinal metastases can result from local tumor activity, pressure on neurological structures, and/or impaired mechanical integrity [14]. The Spine Oncology Study Group developed the Spinal Instability Neoplastic Score (SINS) to assess the degree of spinal instability in order to guide patient referral [15]. In two retrospective studies, it was shown that a higher SINS, reflecting a higher degree of spinal instability, was associated with radiotherapy failure [16, 17]. This suggests that discriminating mechanical pain from tumor pain could help in identifying patients at increased risk of radiation treatment failure. In order to confirm the retrospective data, a prospective cohort study was conducted to investigate the relationship between the degree of spinal (in)stability and response to radiotherapy.

MATERIALS AND METHODS

Study Design

An observational cohort study including patients with spinal metastases treated with palliative radiotherapy was conducted between July 2013 and January 2015 in two tertiary referral centers in North America and Europe. Institutional review board approval was obtained for both institutions. Patients were prospectively enrolled and followed longitudinally for up to 6 weeks (time window -2/+2 weeks) after treatment and all patients provided written informed consent to participate in this study. All patients from the department of radiation oncology with painful (*ie*, a pain score of at least 2, on a scale of 0–10) thoracic, lumbar, or lumbosacral metastases without invalidating neurological deficits (American Spinal Injury Association [18] E or D without progression) were eligible for inclusion. Patients with multiple myeloma, lymphoma, or a history of surgery to the same anatomic level were excluded. Patient characteristics were collected from medical records at baseline and governmental databases were accessed to retrieve vital statistics. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for reporting of observational cohort studies was used [19].

Measurements

A single senior spine surgeon, specialized in spine oncology, calculated the SINS score using images from routine treatment planning computed tomography (CT) scans, while blinded for radiotherapy outcome. The CT scans were obtained by a 16-detector row CT scanner (Brilliance, Philips Medical Systems, Eindhoven, The Netherlands) or GE LightSpeed RT16 (GE Healthcare, Mississauga, Canada) and were reviewed in standardized settings (window level at 300 Hounsfield Units [HU] and window width at 1,000 HU). The SINS was calculated by the sum of five radiological and one clinical component: spine location, pain, bone lesion quality, spinal alignment, vertebral body collapse, and posterolateral involvement of spinal elements (Table 1) [15]. In case of multiple spinal metastases, the SINS of all lesions within the radiation field was calculated and the highest SINS score was used for analysis. Clinical notes of the radiation oncologist or the referring specialist were reviewed to indicate whether pain was movement-related, occasional, or absent. Pain scores were reported as a number between 0 (indicating no pain) and 10 (worst pain imaginable) at baseline and at fixed points in time after palliative radiotherapy. In addition, analgesic use for the preceding 24 hours was collected at time of recording the pain score. A daily total oral morphine dose was calculated from the reported opioid analgesic consumption. In case a patient did not return the pain questionnaire in time, a trained research nurse contacted the patient by phone after 2 weeks. The response to radiotherapy was determined 4 to 8 weeks after palliative radiotherapy according to the international consensus criteria [20] summarized in table 2. Patients were classified as overall responders if a complete or partial response was achieved. Patients with progressive pain or undetermined response were classified as non-responders. Patients who died within 4 weeks after radiotherapy and patients with unknown pain response were excluded from the final analysis.

Statistical Analysis

Categorical variables were expressed as count and proportions; continuous variables were expressed as mean±standard deviation or median with ranges. Chi-Square tests were used to assess differences in baseline characteristics between responders and non-responders. One-way analysis of variance (ANOVA) tests were used for continuous variables. Logistic regression was used to assess whether SINS (continuous, or binary [SINS $\leq$6 or $\geq$7]) was related to pain response. First, overall pain response (*ie*, complete and partial responses combined) was assessed, followed by in-depth analysis selecting only complete pain responders, as these patients may represent a distinct group of patients with tumor pain only. Variables related to pain response, predefined based on literature and clinical experience, were entered in a multivariable logistic regression model to obtain adjusted odds ratios. These variables were gender, primary tumor (breast/prostate/lung/kidney/other) and performance score (World Health Organization [WHO] 0–2/3–4). A worst-case scenario analysis was performed as sensitivity analysis, assuming that all patients who died or were lost to follow-up experienced no response. We estimated the ability of the preselected clinical variables (*ie*, gender, primary tumor, and performance score) to discriminate between patients with and without pain

response by using the area under the receiver operating characteristics (ROC) curve (AUC), and compared this to the area under the ROC curve when SINS was added to these preselected variables. An AUC of 0.5 indicates no discriminating ability, in contrast to perfect discrimination with an AUC of 1 [21]. The database was analyzed using IBM SPSS statistics for Windows version 23.0 (IBM Corporation, Armonk, NY). Results were considered significant if $p<.05$.

Table 1. Spinal Instability Neoplastic Score[a]

SINS component	Score
Location	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semi-rigid (T3–T10)	1
Rigid (S2–S5)	0
Pain[b]	
Yes	3
No (occasional pain but not mechanical)	1
Pain free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements[c]	
Bilateral	3
Unilateral	1
None of the above	0

0–6 points: stable; 7–12 points: impending unstable; 13–18 points: unstable. In patients with a score of 7 or higher, consultation of a spine surgeon is recommended.
[a]Data adapted from Fisher et al. [16].
[b]Pain improvement with recumbency and/or pain with movement/loading of spine.
[c]Facet, pedicle, or costovertebral joint fracture or replacement withtumor.
Abbreviation: SINS, Spinal Instability Neoplastic Score.

Table 2. Response rate to radiotherapy according to the international consensus [20]

Responders	
Complete response	Pain score of 0 and stable or reduced OMED
Partial response	Pain reduction of 2 points on a 0–10 scale or more and/or OMED reduction by 25% or more
Non-responders	
Pain progression	Increase of 2 points on a 0–10 scale or more above baseline, and/or OMED increased by 25% or more
Indeterminate response	Any response including stable disease that is not captured by complete or partial response or pain progression

Abbreviations: OMED, daily oral morphine equivalent

RESULTS

Between January 2013 and September 2014, 103 patients from the European center and 52 patients from the North American center with painful thoracic, lumbar, or lumbosacral metastases were included. Except for WHO performance score, no significant differences were found regarding patients and disease characteristics between responders and non-responders within the cohort (Table 3). A favorable performance score was associated with a positive treatment response (p=.017). Thirteen patients (8%) died within the first 4 weeks after palliative radiotherapy and 18 patients (12%) were lost to follow-up. Of the patients who died within 4 weeks after radiotherapy, six patients had a SINS score of 7 or higher. In the lost to follow-up group, 16 patients had a SINS score of 7 or higher. Of all assessable patients, 73 (59%) patients had a SINS higher than 7, of which 10 (8%) patients had a SINS higher than 13. The association between SINS and pain response was studied in the remaining 124 patients. Of these 124 patients, 16 (13%) patients experienced a complete response, 65 (52%) patients experienced a partial response, and 43 (35%) patients did not experience a response.

In the multivariate analysis (Table 4) relating SINS to complete *vs.* partial and non-responders demonstrated a significant and independent association when considered as binary variable. Considering the SINS as continuous variable, the association remained significant and independent, yet the association may be marginal given the width of the confidence interval (CI) (adjusted odds ratio 0.78 [95% CI 0.62–0.98]). The median SINS in responders was lower compared with the median SINS in partial or non-responders (6 and 8, respectively, p=.030). Sensitivity analysis also showed a significant and independent association between SINS and complete pain response. Spinal Instability Neoplastic Score improved the area under the ROC curve of complete response in addition to other clinical variables from 0.68 (0.53–0.82) to 0.78 (0.66–0.90) (Figure 1A).

Table 3. Baseline characteristics for responders, non-responders, and patients with an unknown outcome

	Response status			
	Responders (n=81) *n (%)*	Non-responders (n=43) *n (%)*	Unknown (n=31) *n (%)*	p value
Gender				0.301[b]
Male	45 (56)	24 (56)	22 (71)	
Female	36 (44)	19 (44)	9 (29)	
Age ± (mean SD)	65 ± 10.9	67 ± 11.8	67 ± 11.1	0.429
Primary tumor				0.245
Breast	25 (31)	8 (19)	4 (13)	
Prostate	17 (21)	15 (35)	7 (23)	
Lung	15 (19)	9 (21)	9 (29)	
Kidney	8 (10)	1 (3)	2 (7)	
Other	16 (20)	10 (24)	9 (29)	
Performance status				0.017
WHO 0–2	78 (96)	35 (81)	26 (84)	
WHO 3–4	3 (4)	8 (19)	5 (16)	
Location				0.143
Thoracic spine	39 (48)	15 (35)	7 (23)	
Lumbosacral spine	42 (52)	28 (65)	24 (77)	
Schedule				0.273
1 x 8 Gy	49 (61)	33 (77)	20 (65)	
5 x 4 Gy	15 (19)	5 (12)	7 (23)	
10 x 3 Gy	14 (17)	2 (5)	2 (7)	
Other	3 (4)	3 (7)	2 (7)	

[a]Pearson Chi-Square.
[b]One-way ANOVA.
Abbreviations: ANOVA, analysis of variance; WHO,World Health Organization; Gy, Gray.

Table 4. Association between Spinal Instability Neoplastic Score (SINS) and complete response status in patients with symptomatic spinal metastases

SINS	Complete response (n=16)	Partial or non-response (n=108)	Unadjusted OR (95% CI)	p value	Adjusted[a] OR (95% CI)	p value
Continuous SINS[b]			0.80 (0.64–0.99)	0.40	0.78 (0.62–0.98)	0.030
Median (range)	6 (3–13)	8 (2–15)				
Median ± SD	6.7 ± 2.8	8.3 ± 2.8				
Binary SINS[c]	*n (%)*	*n (%)*				
Stable	10 (62)	31 (29)	1.00		1.00	
(Impeding) unstable	6 (38)	77 (71)	0.24 (0.08–0.72)	0.11	0.21 (0.06–0.67)	0.009

[a]Adjusted for gender, tumor, and performance status.
[b]SINS modeled as continuous variable ranging from 0–18.
[c]SINS modeled as binary variable 0–6 points vs. 7–18 points.
Abbreviations: CI, confidence interval; OR, odds ratio; SINS, spinal instability neoplastic score.

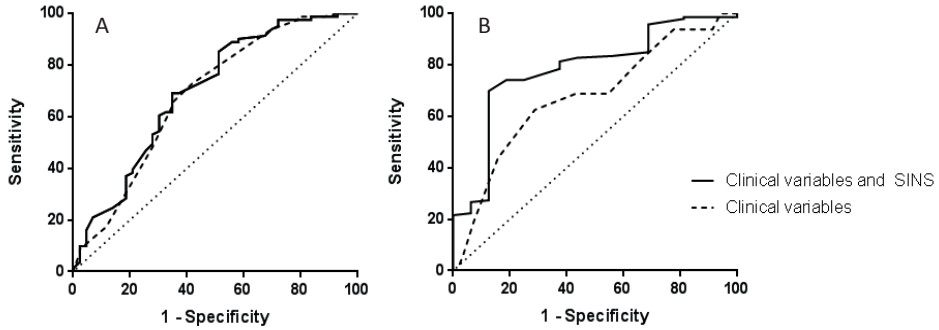

Figure 1. Receiver operating characteristics curves for the discriminative value of clinical variables (gender, primary tumor, and performance status, dotted line), and Spinal Instability Neoplastic Score in addition to those clinical variables (solid line) in predicting overall pain response (A) and complete pain response (B).

In contrast, the multivariate analysis relating SINS to overall pain response *vs.* no response demonstrated no significant and independent association, whether considered continuous or binary (Table 5). The median SINS was similar in non-responders compared to responders (7 and 8, respectively, p=.449). Analyzing the six components of the SINS, no significant differences were found between the responders and the non-responders (location, p=.107; pain, p=.751; lesion, p=.642; alignment, p=.323; collapse, p=0.587; and involvement, p=.908). Sensitivity analysis showed similar results, with no association between SINS and radiotherapy failure. Spinal Instability Neoplastic Score improved the prediction of overall response in addition to other clinical variables only marginally: the area under the ROC curve increased from 0.68 (0.60–0.79) to 0.70 (0.60–0.80) (Figure 1B).

Table 5. Association between Spinal Instability Neoplastic Score (SINS) and overall response status in patients with symptomatic spinal metastases

SINS	Response (n=81)	Non-response (n=43)	Unadjusted OR (95% CI)	p value	Adjusted[a] OR (95% CI)	p value
Continuous SINS[b]			0.91 (0.80–1.04)	0.166	0.94 (0.81–1.10)	0.449
Median (range)	7 (2–15)	8 (2–15)				
Median ± SD	7.8 ± 2.8	8.6 ± 2.9				
Binary SINS[c]	*n (%)*	*n (%)*				
Stable	29 (36)	12 (28)	1.00		1.00	
(Impeding) unstable	52 (64)	31 (72)	0.70 (0.31–1.56)	0.375	0.88 (0.36–2.15)	0.782

[a]Adjusted for gender, tumor, and performance status.
[b]SINS modeled as continuous variable ranging from 0–18.
[c]SINS modeled as binary variable 0–6 points vs. 7–18 points.
Abbreviations: CI, confidence interval; OR, odds ratio; SINS, spinal instability neoplastic score.

DISCUSSION

In this prospective multi-institutional cohort study, we found an association between spinal stability, as reflected by a SINS score lower than 7, and a complete pain response after radiotherapy. When considered as a continuous variable, the association between SINS and a complete pain response might be marginal, given the width of the CI. However, the association of the binary SINS score with a complete pain response is more important, as it is advised that patients with a SINS score of 7 or higher are to be referred to a spinal surgeon for evaluation. No association between SINS and overall pain response could be demonstrated. These results are in line with two previous retrospective studies demonstrating a statistically significant relationship between an increasing SINS score and a higher risk of radiotherapy failure [16, 17]. In the retrospective study of Huisman *et al.*, the odds of radiotherapy failure for a potentially unstable (SINS 7—12) or unstable (SINS 13—18) lesion was respectively 5.9 and 12.8 times higher compared with a stable lesion [16]. Their study, however, used radiotherapy failure, defined as the need for retreatment on the index site, as the main treatment outcome. Patients who did not achieve a response but were physically not fit enough to receive retreatment or patients who declined retreatment were therefore not accounted for. In the current work, a cohort study was performed with prospectively measured radiotherapy response at 4–8 weeks post-treatment according to the international consensus guidelines for palliative radiotherapy [20]. Therefore, all patients, even the patients with debilitating physical condition, could have been followed prospectively. Lam *et al.* investigated predictive factors for the occurrence of spinal adverse events (SAE) after palliative radiotherapy in a retrospective study including 299 patients [17]. Spinal adverse events were defined as interventions to achieve pain relief after fractures or uncontrolled pain despite radiation treatment, indicating a failed pain response after conventional radiotherapy. During the study period, 98 SAEs were reported in 51 patients. A SINS of 11 or higher was shown to be independently associated with a higher incidence of SAEs with a hazard ratio for first SAE of 2.52 (95% CI 1.29–4.92) [17]. These results underscore the importance of the assessment of spinal instability in patients who receive palliative radiation treatment.

In contrast to the two retrospective studies, Mitera *et al.* prospectively investigated the relationship between radiological features on computed tomography imaging and overall pain response after conventional external beam radiotherapy [10]. They investigated radiological parameters partially overlapping the parameters of the SINS score, including lesion type, presence of kyphosis, vertebral body collapse, and involvement of the posterior elements. A total of 33 patients were included and pain response was measured using the international consensus guidelines [20]. Six patients showed a response at 1 month, but no (significant) relationship between radiological parameters and overall pain response was found.

An impaired performance status is a known risk factor for decreased radiotherapy response [7, 13], as was confirmed in our study. Moreover, Yates *et al.* demonstrated that a lower performance

status was associated with short-term survival, explained by a rapid decline in performance status within the last 2 months of life [22]. The rapid decline in performance status might be due to a widespread burden of disease in the terminal phase of cancer. The association between a low performance status and impaired radiotherapy response might, therefore, be explained by this widespread burden of disease; as a local treatment modality, radiotherapy will not provide systemic control and subsequently pain control. Patients with a complete pain response might differ from patients with a partial pain response in their burden of disease. This, therefore, might explain why we found an association between a low SINS score and complete response, but not between SINS and overall response. Another explanation why we found an association between a low SINS score and a complete response might be that these patients represent a true group of patients without (pain due to) mechanical instability, supporting our hypothesis that pain mainly caused by mechanical instability responds less well to radiotherapy than pain caused by local tumor effects.

The current study has several methodological strengths. First, this study was conducted prospectively using an international multicenter cohort design enhancing generalizability of the results. There were some differences in fractionation schedule between the two institutions, but these are unlikely to have influenced the results, as single-fraction and multifraction have shown to be equally effective for the treatment of spinal metastases [6]. Secondly, international guidelines for the measurement of radiotherapy response were used, ensuring comparability to other studies. Lastly, SINS was assessed in a standardized way, by an experienced observer who was blinded for treatment outcome. One observer was deemed sufficient as the literature demonstrated excellent reproducibility of the SINS score [23].

We acknowledge that this study has some limitations as well. First, there were a limited number of cases with a high SINS score indicating spinal instability (SINS $\geq$13), which may be due to a low incidence of spinal instability in radiotherapy practice. The low number of cases with a high SINS score limited extensive statistical analyses, but adjusting for the known confounding factors of gender, tumor type, and performance status was performed. Adjusting for these factors demonstrated no significant difference in the CI, confirming the association between a low SINS score and complete radiotherapy response. Another important reason could be the introduction of the SINS in our institutions approximately 2 years before the start of inclusion. Recently, our group demonstrated that after introduction of the SINS, the mean SINS score in a radiotherapy and surgical cohort decreased [24]. This can be explained by increased awareness of the radiation oncologist for spinal instability and subsequent earlier referral to a spine surgeon, resulting in fewer patients with a high SINS score in the radiotherapy cohort. However, this study sample is a realistic representation of the radiotherapy population after introduction of SINS in clinical practice. Second, a substantial number of patients died within the first 4 weeks after radiotherapy or were lost to follow-up. Despite maximized efforts to obtain follow-up information, becoming

lost to follow-up is inherent to the study population, resulting in a relatively large number of patients with an unknown response. Notably, in the current study these patients had high SINS scores. However, the worst-case scenario analysis, assuming no response in all patients with an unknown pain response, confirmed the results of the primary analysis. Lastly, in the current study, only patients with thoracic, lumbar, or lumbosacral metastases were included, limiting generalizability to these locations. The cervical spine has unique biomechanical characteristics compared with the thoracic and lumbar spine, providing stability for the head while simultaneously allowing for a wide range of motion. As a result, the current composition of the SINS score may be less reliable at detecting instability of the cervical spine.

CONCLUSION

The present study used the SINS score, reflecting the degree of spinal (in)stability, as a tool to predict radiotherapy response in patients with spinal metastases. A low SINS score (<7) was associated with a complete pain response to palliative radiotherapy. However, no relation could be demonstrated between the SINS (whether continuous or binary) and overall pain response (*ie*, complete and partial combined) to radiotherapy. Spinal Instability Neoplastic Score was developed to help identify spinal neoplastic-related instability, with the main purpose of guiding referrals and improving communication rather than providing a prognostic tool for treatment outcome. As necessary for a referral tool, the SINS score includes both components quantifying the present degree of spinal instability (*eg*, spinal malalignment) as well as components reflecting the future risk of spinal instability (*eg*, lytic aspect of the lesion). This decreases, however, the applicability of the SINS as a prediction tool. Translating the results of the current study in clinical practice, patients with a low SINS score indicating no spinal instability can effectively be treated with palliative conventional external beam radiotherapy. However, it is advised that patients with a SINS score of 7 or higher be referred to a spinal surgeon to evaluate if surgical intervention is indicated as currently recommended by the SINS [15]. Although the majority of these patients will achieve a (partial) response after radiotherapy, some patients might benefit more from surgical intervention, whether or not combined with postoperative irradiation, as radiation therapy outcomes in these patients is less predictable. Future studies should be directed at optimizing the definition of spinal neoplastic-related (in)stability if it is to be used as a tool to predict treatment outcome.

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CHAPTER 5

Inter-observer agreement in GTV delineation of bone metastases on CT and impact of MR imaging: A multicenter study

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ABSTRACT

Background and purpose

The use of Stereotactic Body Radiotherapy (SBRT) for bone metastases is increasing rapidly. Therefore, knowledge of the inter-observer differences in tumor volume delineation is essential to guarantee precise dose delivery. The aim of this study is to compare inter-observer agreement in bone metastases delineated on different imaging modalities.

Material and methods

Twenty consecutive patients with bone metastases treated with SBRT were selected. All patients received CT and MR imaging in treatment position prior to SBRT. Five observers from 3 institutions independently delineated gross tumor volume (GTV) on CT alone, CT with coregistered MRI and MRI alone. Four contours per imaging modality per patient were available, as one set of contours was shared by 2 observers. Inter-observer agreement, expressed in generalized conformity index [CIgen], volumes of contours and contours center of mass (COM) were calculated per patient and imaging modality.

Results

Mean GTV delineated on MR (45.9 ± 52.0 cm^3) was significantly larger compared to CT–MR (40.2 ± 49.4 cm^3) and CT (34.8 ± 41.8 cm^3). A considerable variation in CIgen was found on CT (mean 0.46, range 0.15–0.75) and CT–MRI (mean 0.54, range 0.17–0.71). The highest agreement was found on MRI (mean 0.56, range 0.20–0.77). The largest variations of COM were found in anterior–posterior direction for all imaging modalities.

Conclusions

Large inter-observer variation in GTV delineation exists for CT, CT–MRI and MRI. MRI-based GTV delineation resulted in larger volumes and highest consistency between observers.

INTRODUCTION

Bone metastases are a common manifestation of cancer and pain is the most prevalent symptom [1]. Pain has a major influence on quality of life [2]. Conventional radiotherapy is the cornerstone in the management of bone metastases, but the use of Stereotactic Body Radiotherapy (SBRT) is increasing rapidly [3]. Conventional radiotherapy is effective in achieving pain relieve in 60% of the patients with bone metastases, but unfortunately up to 40% of the patients do not achieve sustainable pain relief after receiving conventional radiotherapy [4]. SBRT can result in longer duration of symptom relief together with improved local control and a potential for delayed disease progression [5]. The efficacy and toxicity of this treatment depend on many factors including target definition, dose fractionation, tumor volume margins, proximity to organs-at risk, and dose-delivery technique. Currently, multiple randomized controlled trials are evaluating the effectiveness of SBRT over conventional radiotherapy in patients with bone metastases [6–8]. SBRT involves high precision dose delivery to the target volume while sparing healthy tissues. Accurate and consistent delineation of the target volume is therefore crucial in SBRT. In daily clinical practice, computed tomography (CT) is the standard imaging modality for target volume delineation in patients with bone metastases. CT offers excellent bony detail, but magnetic resonance imaging (MRI) provides increased visibility of soft tissue structures. The value of MRI in target volume definition in bone metastases is not established yet. Knowledge of the inter-observer differences in tumor volume delineation is essential to guarantee accurate and precise dose delivery. The aim of this study is to assess inter-observer agreement in delineation of bone metastases on CT, CT with coregistered MRI and MRI alone.

METHODS

This study was designed and reported according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [9].

Patient selection

All consecutive patients with bone metastases treated with SBRT at our center between November 2014 and December 2015 were screened for eligibility for this study. These patients are participants in the PRESENT study. The PRESENT study is a prospective cohort in which all patients with bone metastases treated at the department of radiation oncology and orthopedic surgery are enrolled [7]. Patients had to fulfill the following criteria for inclusion: bone metastases treated with SBRT, availability of CT and MR imaging in treatment position, visibility of the metastases on both imaging modalities. In case of multiple lesions, one metastasis was randomly selected for delineation.

Imaging technique and data acquisition

CT and MR imaging was performed prior to radiotherapy in treatment position. Patients were immobilized with an individual vacuum cushion (BlueBAGTM, Elekta, Stockholm, Sweden). CT images were obtained with a Philips large bore CT scanner (Philips Medical Systems, Cleveland, OH) with 1 mm slice thickness. A 1.5 Tesla MRI scanner (Achieva; Philips Medical System, Best, The Netherlands) was used to acquire T1- and T2-weighted turbo spin echo (TSE) images in transverse direction for every patient. Depending on the clinically used scan protocol, coronal and/or sagittal images were acquired, including 3D T1 fast field echo (FFE) mDIXON scan with slice thickness 1.1 mm and diffusion weighted imaging (DWI) with slice thickness 4 mm (Table A1 in the supplement). No intravenous contrast was used. The MRI to CT registration procedure consisted of defining a rectangular box of interest containing the GTV and using a mutual information registration algorithm within this volume. This method is done according to the clinical practice at our department.

Target volume delineation and observers

Five observers, two radiation oncologists and three radiation oncology residents, from three institutions independently delineated the gross tumor volume (GTV) after a training set of two patients and a subsequent consensus meeting. Three observers rated all 20 cases, and two observers from the same institution shared delineation of 20 cases (*ie*, WSCE delineated case 1–13 and NK delineated case 14–20). The GTV was delineated according to our institutional protocol (Table 1), using an in-house developed delineation and data analysis software tool [10]. Observers received information about the primary tumor site, relevant medical history, location of the metastases and presenting symptoms. First, GTV was contoured on CT-images using a recommended window/level setting of 2000/500 Hounsfield units with the option to make adjustments to this setting if deemed necessary to resemble daily practice. CT delineation was followed by delineation on CT with co-registered MR images with the previous contours available. Finally, MRI delineation was performed after an interval of at least four weeks to avoid recall of prior delineations. MRI only delineations were performed on the transversel T1 image and observers were allowed to consult other sequences. Observers were instructed to record delineation time, image quality (good, moderate, poor), difficulty of contouring the target areas on all imaging modalities (five point scale: very difficult – very easy) and MRI sequences used for contouring.

Table 1. Target volume delineation in spinal and non-spinal lesions

	Spinal lesions	Non-spinal lesions
Part of GTV	Extra-osseous disease	Extra-osseous disease Edema
Excluded from GTV	Discs Edema Osteophytes	Joints

GTV: gross tumor volume. Target volume definition according to institutional protocol and observer consensus meeting.

Data analysis

Volume of contours, conformity index and center of mass (COM) were calculated to evaluate agreement between observers and differences in location of contours. Volumes of contours were calculated per observer, per patient and per imaging modality and average volumes were computed per case and per imaging modality. To assess the overlap between all possible observer pairs, the generalized conformity index $CI\ gen = \frac{\sum pairsij\ |Ai \cap Aj|}{\sum pairsij\ |Ai \cup Aj|}$ was calculated per case and imaging modality [11]. A CIgen of 1 implies perfect agreement among observers, while CIgen = 0 means no overlap between the delineations. For visual comparison of interobserver agreement count maps were generated, *i.e.* maps of voxels showing the number of enclosing observer delineations, for each case and imaging modality. The center of mass (COM) of each delineated volume was used to assess differences in contour locations. Differences in COM were calculated for each observer pair and were expressed as the length of a three-dimensional vector (*ie,* the distance of center of the mass [dCOM]). Moreover, to provide information about the direction of variation in contour location, the maximum differences of COM between the observers in all three directions were presented. Subgroup analyses were performed for patients with spinal and non-spinal bony lesions. The Wilcoxon signed rank test was used to analyze statistical significant differences with a p value of <0.05 indicating statistical significance.

RESULTS

Patients and observers

Twenty consecutive patients with bone metastases treated with SBRT were included (Table 2). Most common primary tumor sites were breast (n = 6) and prostate (n = 5). The metastatic bone lesions were both spinal (n = 11) and non-spinal (n = 9). Image quality was considered moderate to good for all CT and MR images by the observers. Observers experienced most difficulties in delineating on CT only images. Delineation on CT–MR images was considered easier than on MRI only. For each case, three to five MRI sequences were used for delineation. The transversal T1-weighted TSE (all cases, 100%), T2-weighted TSE (63/80 cases, 79%) and DWI (43/80, 54%) sequence were mostly used. Delineation time varied from 1 to 60 min per case. Contouring on CT–MR images was most time-consuming with an average of 18 min (range 3–60) per case, followed by 14 min (range 1–40) on MRI only, and 12 min (range 1–35) on CT images only.

Volumetric analysis

Tumor delineation on MR imaging resulted in significantly larger mean volumes (45.9 ± 52.0 cm^3) compared to CT–MRI (40.2 ± 49.4 cm^3, p = 0.011) and CT (34.8 ± 41.8 cm^3, p = 0.002). (Figure 1, Table 2). Delineations on CT–MRI were significantly larger compared to CT (p = 0.007).

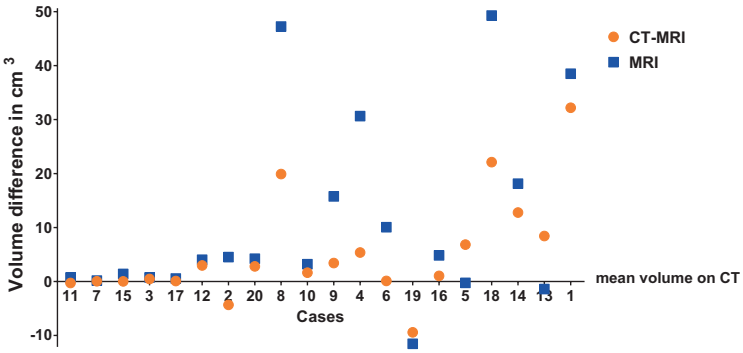

Figure 1. Absolute volume differences in cm^3 of GTV delineations, based on CT–MR and MR only compared to the mean volume of the lesion delineated on CT (X-axis), derived from contours of all observers. Cases are arranged from the smallest mean volume on CT (case 11: 1.2 cm^3) to the largest volume on CT (case 1: 184.7 cm^3). Cases 8 and 18: the volume difference on CT–MRI compared to CT only and MRI only compared to CT–MRI is similar. Case 5 and 13: the MRI volume mimics the CT volume, while on CT–MRI the volume increases in both cases. Case 19 is an outlier with the highest volume on CT imaging and a decrease in volume on CT–MRI and even more on MRI.

Table 2. Overview of GTV and generalized conformity indices per case and modality

			Mean volume in cm^3 (SD)			CIgen		
Case	Primary tumor	Location	CT	CT-MRI	MRI	CT	CT-MRI	MRI
11	prostate	iliac bone	1.2 (0.6)	0.9 (0.3)	2.0 (2.2)	0.45	0.52	0.20
7	prostate	sacrum	1.4 (1.1)	1.4 (1.0)	1.5 (0.7)	0.36	0.39	0.37
15	breast	iliac bone	2.6 (0.9)	2.6 (1.1)	4.0 (3.4)	0.43	0.50	0.31
3	melanoma	femur head	3.3 (3.5)	3.7 (1.7)	4.0 (0.7)	0.25	0.51	0.67
17	thyroid	thoracic spine	4.3 (1.6)	4.4 (0.9)	4.8 (0.7)	0.53	0.59	0.65
12	prostate	thoracic spine	7.2 (3.4)	10.2 (3.3)	11.2 (3.0)	0.47	0.52	0.55
2	breast	lumbar spine	12.5 (8.1)	8.2 (3.9)	17.0 (10.2)	0.15	0.17	0.37
20	colon	thoracic spine	14.0 (6.7)	16.8 (4.1)	18.2 (2.9)	0.37	0.60	0.66
8	lung	thoracic spine	22.0 (9.7)	41.9 (17.4)	69.2 (31.0)	0.46	0.48	0.47
10	renal	thoracic spine	22.3 (8.9)	23.9 (6.4)	25.5 (5.8)	0.52	0.61	0.63
9	breast	lumbar spine	26.5 (9.7)	30.0 (6.4)	42.3 (14.1)	0.59	0.63	0.55
4	prostate	thoracic spine	31.3 (23.8)	36.7 (5.7)	62.0 (17.5)	0.34	0.64	0.61
6	prostate	lumbar spine	36.7 (5.2)	36.8 (15.7)	46.7 (13.6)	0.32	0.47	0.56
19	breast	iliac bone	39.1 (8.4)	29.7 (12.0)	27.6 (6.8)	0.73	0.58	0.69
16	lung	thoracic spine	39.7 (4.8)	40.8 (5.3)	44.6 (7.0)	0.69	0.71	0.68
5	renal	iliac bone	51.2 (19.3)	58.0 (20.0)	50.9 (27.9)	0.60	0.52	0.49
18	breast	pelvis	62.7 (41.0)	84.8 (34.2)	112.0 (32.2)	0.37	0.53	0.64
14	esophageal	iliac bone	66.8 (10.4)	79.6 (10.4)	84.9 (19.2)	0.66	0.61	0.60
13	breast	pelvis	67.5 (19.9)	75.9 (20.2)	66.1 (17.3)	0.67	0.58	0.64
1	renal	iliac bone	184.7 (9.2)	216.9 (41.3)	223.2 (28.6)	0.75	0.71	0.77
	Mean (SD)		34.8 (41.7)	40.2 (49.4)	45.9 (52.0)	0.49	0.54	0.56
	Median		24.4	29.8*	34.9*	0.46	0.55*	0.61

Cases ranked on mean delineated volume on CT by 4 observers. GTV: gross tumor volume, CIgen: generalized conformity index, SD: standard deviation * Statistical significant compared to CT.

Inter-observer agreement

A large variation in CIgen was found for all imaging modalities, indicating differences in interpretation of GTV. Delineation on CT resulted in the lowest mean CIgen (0.46, range 0.15–0.75), compared to CT–MRI (0.54, range 0.17–0.71) and MRI (0.56, range 0.20–0.77) (Figure 2). CIgen was significantly higher on CT–MRI compared to CT ($p = 0.048$), but not significantly higher on MRI *vs.* CT ($p = 0.156$) and MRI *vs.* CT–MRI ($p = 0.279$) (Table 2). In Figure 3, examples of GTV delineations of the four observers are presented in count maps on all three imaging modalities.

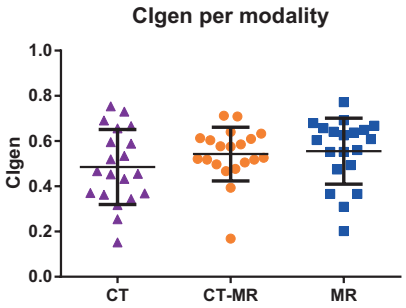

Figure 2. Generalized conformity index (CIgen) per modality.

Location of contours

Median dCOM was 3.7 mm on CT, 4.0 mm on CT–MRI and 3.3 mm on MRI. Median dCOMs were not significantly different between modalities ($0.179 < p < 0.341$). The largest variations between observers were in anterior–posterior (AP) direction, with a median maximum distance of COM of at least 3 mm on all imaging modalities (Table A2 in the supplement). The maximum difference in the observer pairs was 24 mm. The smallest median variation in COM between observers was seen in MRI delineations in left–right (LR) (1.9 mm) and AP direction (3.0 mm). In craniocaudal (CC) direction, the smallest median variation in COM was observed on CT imaging (Table A2).

Spinal versus non-spinal metastases

A subgroup analysis was performed in spinal *vs.* non-spinal lesions. The mean delineated volumes in spinal lesions were considerably lower in comparison to delineations of non-spinal lesions. In spinal lesions, there was a significant increase in contoured volume on CT–MRI (22.8 ± 15.3 cm^3, $p = 0.033$) and MRI (31.2 ± 23.0 cm^3, $p = 0.003$) compared to the volume on CT (19.8 ± 13.0 cm^3). Agreement between observers, expressed in CIgen, was significantly better on CT–MRI (mean 0.53, range 0.17–0.71, $p = 0.003$) and MRI (mean 0.55, range 0.33–0.68, $p = 0.016$). No significant differences in volume or CIgen were observed in non-spinal lesion between the imaging modalities (Table 3).

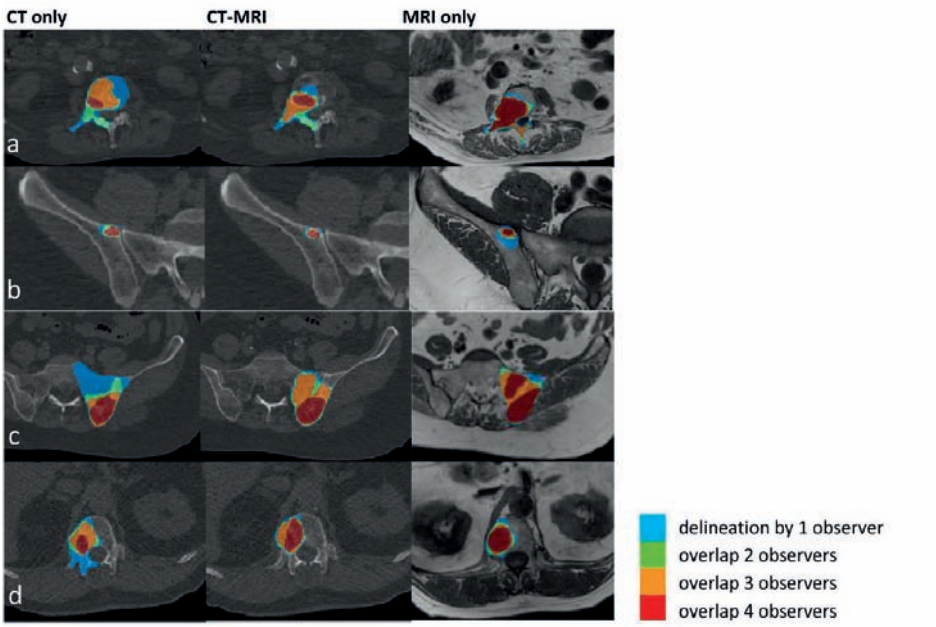

Figure 3. Delineations of 4 observers on transverse CT, CT with co-registered MRI sequences (visualized on CT) and T1-weighted MR images in 4 patients. a: case 6, b: case 11, c: case 18, d: case 20.

DISCUSSION

In this study, 5 observers contoured the GTV of bony lesions in 20 patients treated with bone SBRT on CT, CT–MRI and MRI. Four contours per imaging modality per patient were available, as one set of contours was shared by 2 observers. A significant increase in target volume was seen when MR images were co-registered to CT images and the largest volumes were seen on MR images. A large variation in the generalized conformity index was found for all imaging modalities with highest inter-observer agreement when delineated on MR images. For all modalities, the maximum difference in center of mass was the largest in the anterior–posterior direction. Remarkably, addition of MRI improved the CIgen for spinal lesions significantly, but not for non-spinal lesions.

To our knowledge, this is the first study investigating interobserver agreement in delineation of bone metastases in multiple imaging modalities for SBRT purposes. In the palliative setting, only Grabarz *et al.* [12] investigated target definition interobserver agreement. Their study consisted of 9 palliative cases (including 3 bone metastases, 3 palliative lung cancer, and 3 abdominal pelvic soft-tissue disease cases) delineated by 5 observers. All observers were asked to define treatment fields on 2D and 3D-based planning. Overlap in target volume between observers varied from 57% in bone metastases, 65% in lung lesions to 66% in abdominal cases. Grabarz *et*

al. [12] concluded that interobserver variation for conventional radiotherapy on CT images was considerable but as no explicit GTV delineation was involved, they could not draw conclusions about GTV delineation.

In our study, we chose an approach that closely resembles daily clinical practice. The closer experimental conditions are to 'real life', the more applicable the results will be in the clinical setting. Furthermore, the international multi-institutional nature of this study will increase the applicability of our findings to other radiation oncology institutions. We acknowledge that there are certain consequences to this approach. The observers are experienced (WSCE, NK) and less experienced (CLT, JMV, GF) in GTV delineation in bone metastases. Since both experienced authors did not delineate the same cases, it is not possible to compare trainees *vs.* experienced radiation oncologists. For example, when considering the delineated volume as metric, significant differences are found between experienced observers and between trainees but differences between experienced observer and trainee were not always significant.

Most observers have ample experience using MRI for contouring in spinal metastases, while the use of MRI for contouring purposes in non-spinal bone metastases is not established yet. Furthermore, the observers were trained in different institutions with other delineation protocols and software and the trainee delineations were not peer-reviewed by an experienced radiation oncologist. We compensated for all these issues by arranging a consensus meeting. As mentioned, despite the consensus meeting, agreement on all modalities was rather low.

One of the main findings of this work is the target volume increase when using or adding MR images. This increase might be explained by better visibility of extra-osseous disease or bone marrow infiltration on MR imaging [13]. Our findings are consistent with previous studies that compared CT and MR target volume delineation for radiotherapy treatment planning at other

Table 3. Target volume in cm^3 and generalized conformity index (CIgen) in spinal and non-spinal lesions

	CT	CT-MRI	MRI
Spinal lesions (n=11)			
Mean volume in cm^3 (SD)	19.8 (13.0)	22.8 (15.3)*	31.2 (23.0)*
Median volume in cm^3	22.0	23.9	25.5
Mean generalized CI (range)	0.44 (0.15- 0.69)	0.53* (0.17-0.71)	0.55* (0.33-0.68)
Non-spinal lesions (n=9)			
Mean volume in cm^3 (SD)	53.2 (56.7)	61.4 (67.8)	63.9 (71.3)
Median volume in cm^3	51.2	58.0	50.9
Mean generalized CI (range)	0.55 (0.25-0.75)	0.56 (0.50-0.71)	0.56 (0.14-0.80)

SD = standard deviation. * Wilcoxon signed ranks test $p < 0.05$

sites [14,15]. With a lack of a reference standard in the form of pathological validation it is impossible to know how well contours represent the actual tumor. In this study we assumed that the areas delineated by multiple observers contain tumor. Because of the lack of pathological validation, we focused on identifying agreement of GTV delineation and not accuracy, *ie.* regions that truly contain tumor.

In our study, inter-observer agreement was found to be rather low for all imaging modalities, despite the use of delineation guidelines. This difference in GTV interpretation might be caused by different levels of delineation experience between observers and contouring habits. The highest agreement was found in MRI contouring alone, but was not statistically different compared to CT alone delineation. This might be explained by large ranges of CIgen leading to overlap in confidence intervals as shown in Figure 2. Although agreement in our study was improved using CT–MRI and MRI compared to CT imaging, this does not necessarily mean that the use of MR imaging leads to better treatment response in patients with bony metastases. Previous studies concerning inter-observer agreement of GTV contouring on CT and MR images in a curative clinical setting reported contradicting findings [16]. Most studies showed a significant improvement of agreement between observers when MRI is used for delineation [15,17–21] while other studies showed no statistical difference [14,22,23]. These non-significant statistical differences in agreement might be explained by the small amount of cases included in these studies (5–15 cases) or by the co-registered sequences used for delineation. Except for Den Hartogh *et al.* [15] and Giezen *et al.* [22], the sequences used are not mentioned in the articles. In general, a wide variety of metrics are used in analyzing interobserver agreement in delineation studies [24]. Volume and conformity index are the most commonly reported metrics in delineation studies [25]. However, these metrics provide no information on the location of the delineated volumes. To overcome the lack of position information, COM variations and dCOM were added to our analysis. Since the dCOM is expressed as a vector, we decided to add the maximum COM differences between observer pairs, to study the direction of difference in contouring in more detail.

The subgroup analysis for spinal and non-spinal bony lesions demonstrated increased target volumes and improvement of CIgen on MR imaging in spinal lesions. Spinal metastases have a clearly defined clinical tumor volume (CTV) [26], while the CTV is not well established in non-spinal bony lesions. As irradiating the entire involved bone is not possible in most cases, the CTV in non-spinal bony lesions will be derived from the GTV. Thus, in most non-spinal cases, the CTV will be an expansion of the GTV. Variation in the interpretation of GTV in non-spinal metastases will therefore reflect on the magnitude of the CTV. Unfortunately, in non-spinal bony metastases, our study demonstrated that MR images did not improve GTV agreement between observers. This might induce a considerable amount of variation between practices and practitioners.

Multiple bone SBRT strategies are available. At our institution, it is common to boost the GTV while prescribing a lower dose to the non-affected surrounding bone, *i.e.* a simultaneous integrated boost (SIB) approach. Previous studies concluded that interobserver variation in target volume delineation is the biggest contributor to uncertainty in radiation treatment planning [24,27] which influences all the treatment fractions in the same way (systematic error). Systematic errors cause a shift of the cumulative dose distribution relative to the target resulting in the GTV possibly moving outside the high dose region. The dosimetric consequences of the found inter-observer disagreement on GTV delineation have not been investigated. Using a SIB technique, it is even more important that observers agree on the definition of the GTV. Inaccurate delineations of the latter will result in either small volumes that do not contain the whole tumor volume, leading to a suboptimal effect on pain and local control or large volumes that will unnecessarily increase the dose on healthy tissues and increase fracture risk [28]. In the PRESENT cohort, the VERTICAL randomized controlled trial comparing conventional radiotherapy with SBRT in patients with spinal metastases is running at our department [7]. Within this trail, evaluation on the clinical outcome of the patients treated with SBRT is planned. This evaluation will help putting the results of the inter-observer GTV delineation study in a clinical prospective.

Regarding improving the GTV delineation consistency, at our institute the delineations are always discussed by a second radiation oncologist before the patient is treated given the importance of peer review [29,30].

Given that SBRT is a novel technique for management of bone metastases, there are no standardized guidelines for GTV contouring and utilization of imaging modalities. Cox *et al.* [26] provided a consensus guideline for spine radiosurgery based on expert opinion. Besides a remark about including epidural and paraspinal components in the GTV, there is no consensus about whether to add for example edema, disks or osteophytes to the GTV. Historically, CT imaging is used for contouring bone metastases. However, this might change as MRI is able to visualize better the extent of disease by better soft tissue contrast compared to the CT [31]. MRI is a modality with different imaging sequences focusing on different aspects of tissue. In this study, transverse T1-weighted TSE, T2-weighted TSE and DWI sequences were mainly used for target definition. In other studies the information about MR sequences is frequently missing. For example, Thibault *et al.* [32] surveyed 13 spine experts in SBRT treatment planning in spinal metastases. The survey demonstrated that all centers used MRI for treatment planning, but no information about the used sequences was provided. Byun *et al.* [33] investigated the role of DWI in response evaluation after conventional spine radiotherapy in 24 patients. A relation was found between response and DWI signal intensity indicating that DWI sequences might play a valuable additional role in target definition. In our study, in 60–100% of the cases the DWI sequence was viewed during delineation of the target volume. In 40% of the cases, the observer subsequently used the DWI sequence to modify the contours.

MRI-based delineation in bone metastases is relatively new, but with technological advancement, MRI-guided radiation therapy can be introduced in the clinical setting. At our institution, the MR linac, soon to be clinically implemented, allows treatment of patients without the need of CT imaging [34]. The MR linac treatment workflow demands standardized MRI sequences and delineation procedures. The results of our study show that delineation consistency on MRI most favorable, which is promising for further implementation of MR guided radiotherapy in the treatment of bone metastases.

In conclusion, this study demonstrated substantial interobserver variation in GTV delineation for all investigated imaging modalities. Delineation of GTV on MR imaging resulted in larger volumes and better agreement between observers, particularly in spinal lesions. Also, the smallest variations in direction of COM where seen on MRI. These results indicate that the highest consistency between observers is seen when MR imaging is used. Future research should focus on strategies to further reduce variability in GTV delineation in bony metastases and on assessing the clinical impact of MRI-based delineation.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest to disclose.

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APPENDICES

Table A1. MR imaging parameters

MR imaging parameters	MR sequences					
	tT1TSE	sT1TSE	tT1TSE	sT2TSE	DWI	tT1FFE
Sequence	Fast spin echo	Fast spin echo	Fast spin echo	Fast spin echo	Single shot spin-echo echo-planar imaging	3D spoiled gradient echo
Contrast	T1	T1	T2	T2	Diffusion	T1
Direction	Transverse	Sagittal	Transverse	Sagittal	Transverse	Transverse
Fat suppression	-	-	Multi echo dixon	Multi echo dixon	SPIR	Multi echo dixon
TR/TE (ms)	623/16	658/8	2147/80	4105/80	4367/67	5.7/2.3
Echo train length	8	5	18	18	59	200
B-values (s/mm^2)	-	-	-	-	0/200/800	-
Field of view (mm)	300 x 420	160x 352	300 x 201	350x 199	420 x 300	4530x 400
Acquisition matrix (mm^2)	420 x 406	440 x 337	269 x 376	352 x 348	163 x 165	412 x 412
Slice thickness (mm)	4	4	4	4	4	1.1
Number of slices	25	25	25	50	25	273
Acceleration factor	2.9	1	1	1	2	3.4
Number of averages	2	2	4	2	3/5/7	2
Acquisition time (s)	127	181	360	378	179	304

MR imaging parameters and MRI sequences. cT1w: coronal T1 weighted image, sT1w: sagittal T1 weighted image, tT1w: transverse T1 weighted image, T2w: T2 weighted images. TE : echo time, TR: repetition time.

Table A2. Maximum differences of the center of mass (COM)*in mm between observers

	CT			CT-MRI			MRI		
Case	LR	AP	CC	LR	AP	CC	LR	AP	CC
1	2.7	2.9	5.9	3.1	4.1	6.5	2.4	2.4	2.9
2	14.2	10.5	24.4	16.0	9.3	22.8	7.6	5.2	11.2
3	0.9	1.4	2.6	1.8	1.7	2.8	1.1	0.6	2.7
4	3.0	10.4	7.6	2.8	5.1	2.8	3.8	1.9	2.0
5	2.0	4.7	4.9	3.6	7.4	7.1	0.6	8.5	2.2
6	18.2	20.0	3.8	6.3	10.4	2.1	1.1	5.0	1.0
7	7.1	1.4	1.2	7.6	1.5	1.6	8.9	3.9	1.4
8	4.5	3.8	2.1	5.7	4.0	4.5	4.5	9.4	5.1
9	3.2	3.6	0.5	5.7	4.0	4.5	1.9	4.2	6.4
10	4.3	5.3	2.0	2.6	2.3	1.3	1.2	3.3	1.4
11	2.3	0.5	1.1	2.3	0.7	1.0	0.9	5.0	3.0
12	3.0	5.4	1.6	4.2	2.4	2.7	4.8	2.4	2.3
13	2.8	2.7	2.1	1.9	6.7	3.6	4.6	5.0	2.1
14	2.4	1.6	11.2	2.5	2.6	11.2	2.8	3.7	11.3
15	2.9	4.5	1.8	1.1	1.8	1.3	1.9	1.4	5.5
16	2.5	2.0	1.5	0.4	1.2	2.7	0.3	1.9	2.1
17	4.8	1.1	0.8	2.0	1.3	1.4	0.7	0.7	2.0
18	3.5	15.4	9.7	3.0	12.0	8.9	4.0	2.6	5.4
19	1.7	1.1	0.9	1.1	3.0	1.7	1.1	2.0	0.6
20	1.5	11.5	1.0	3.0	3.7	2.1	1.7	2.5	4.2
median	2.9	3.7	2.0	2.9	3.3	2.7	1.9	3.0	2.5

*For all 20 patients, the COM was calculated. COM is based on information of three directions x, y, and z, representing left-right (LR), antero-posterior (AP) and cranio-caudal (CC). This table shows the maximum difference in COM between in each direction. The differences were not statistically significant.

CHAPTER 6

The use of a simultaneous integrated boost in spinal stereotactic body radiotherapy to reduce the risk of vertebral compression fractures: A treatment planning study

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ABSTRACT

Purpose

Vertebral compression fractures (VCF) are a common complication after spine SBRT. We propose a simultaneous integrated boost (SIB) approach designed to spare bone surrounding the metastasis to mitigate the VCF risk. The dosimetric feasibility for SIB SBRT was compared with non-SIB SBRT treatment plans.

Methods and Materials

SIB and non-SIB SBRT plans were created for 12 spinal lesions. For SIB plans, doses of 18 Gy to the metastasis (PTVb) and 8 Gy to the surrounding bony compartment (PTVe) were prescribed; 18 Gy to the PTVe was prescribed in non-SIB plans. Treatment plans were optimized for adequate coverage and organs at risk constraints.

Results

For SIB SBRT plans, median coverage of the PTVb was 95% (range, 80–100%) which was significantly higher compared to the coverage of the non-SIB SBRT plans (92%, range 75–100%). In SIB SBRT plans, the median mean dose to the PTVe volume was 12 Gy, while this was 17 Gy for the non-SIB SBRT plans. Organs at risk were easier spared in the SIB SBRT approach.

Conclusions

For spinal metastases, SIB SBRT plans allow a substantial dose reduction to the relatively healthy bony compartment. This might reduce the risk of radiation-induced vertebral fractures.

INTRODUCTION

The skeleton is the most common site of metastases in end-stage cancer, with the spine being the most frequent location [1]. Metastatic spinal disease may present with severe back pain, neurologic symptoms, and instability. In the management of spinal metastases, stereotactic body radiotherapy (SBRT) is an emerging technique intended to deliver a high radiation dose precisely to spinal metastases in a single or a few fractions [2]. Concern has been raised about the extreme dose-fractionation schemes and large biologically effective doses used in spinal SBRT as the risk of vertebral compression fractures (VCF) have been reported to be as high as 40% [3]. In a multi-institutional analysis including 410 spinal segments in 252 patients, the 2-year cumulative fracture incidence was 13.5% [4]. Considering the overall literature with VCF, these rates are much higher compared to conventional palliative external beam radiation treatment, which is typically below 5% [5]. As a result of increasing awareness of VCF as a complication of SBRT, investigators have reported on the utility of spinal instability neoplastic score (SINS) [6] and other factors to identify those at highest risk. Patients with mechanical pain, baseline VCF, lytic tumor, and spinal misalignment are at highest risk for developing VCF [7].

Prevention of these fractures is challenging because the metastatic lesions lie within the segment at risk. The purpose of this study was to investigate a strategy to mitigate the risk of SBRT-induced VCF by boosting the gross tumor volume (GTV) with regard to the non-affected bone included in the clinical target volume (CTV). We hypothesize that dose should be escalated in the GTV itself, while microscopic disease in the CTV can be treated with a conventional dose, based on our understanding of conventional radiotherapy. We report on the dosimetric feasibility of a simultaneous integrated boost (SIB) planning design, specific for patients treated with single fraction spinal SBRT. Furthermore, we compared the SIB treatment strategy with a non-SIB treatment approach.

METHODS AND MATERIAL

Patient selection

Twelve patients with metastatic spinal disease treated with spinal SBRT at the Department of Radiation Oncology of the University Medical Center Utrecht, The Netherlands, between June 2013 and September 2016 were identified. Patients were participants in the prospective PRESENT cohort [8] and signed informed consent for their clinical data to be used for research purposes. Treatment sites ranged from cervical tot sacral lesions in patients without any clinical evidence of spinal cord compression. The 12 cases were chosen in such a way to form a representative selection of our stereotactically treated patient population with regard to tumor volume and location within the spine (Table 1).

Table 1. Patient characteristics

	Primary tumor	Location*	PTVb volume (cc)	PTVe volume, including PTVb volume (cc)	Ratio PTVb volume to PTVe volume (%)	Shortest distance PTVb to spinal cord or cauda (mm)
1	Prostate	C7	3.1	14.3	22	1
2	Prostate	Th1–2	45.3	61.9	73	0
3	Prostate	Th5	2.2	37.6	6	2
4	Prostate	Th8–9	39.9	109.5	36	1
5	RCC	Th9	26.6	61.0	44	1
6	Colon	Th12	32.4	78.8	41	4
7	Breast	L1	2.0	47.4	4	6
8	Breast	L3	74.4	155.4	48	0
9	Melanoma	L4	46.9	84.2	56	0
10	Lung	L4	26.7	80.1	33	1
11	Breast	Sacrum	40.1	336.8	11	0
12	Prostate	Sacrum	3.1	58.6	5	6
Median			29.6	70.4	35	1
Range			2.0–74.4	14.3–366.8	4 – 73	0 – 6

*In the PRESENT patient population treated with spinal SBRT, the contribution of cervical lesions to the entire population was 6%, thoracic lesions 45%, lumbar lesions 39%, and sacral lesions was 10%.
Abbreviations: C, cervical spine; cc, cubic centimeter; L, lumbar spine; mm, millimeter; PTVb, planning treatment volume of the GTVb; PTVe, planning treatment volume of the CTVe; Th, thoracic spine

Definition of treatment volumes and organs at risk

Patients were immobilized in an individual evacuated cushion (BlueBAG^{TM} Vacuum Cushion, Elekta, Stockholm, Sweden) and for lesions down to Th3 fixated in a 5-point thermoplastic mask (Civco Medical Solutions, Kalona, Iowa, USA). CT simulation was performed prior to radiation treatment and in radiotherapy position on a Philips large bore CT Scanner (slice thickness 1.2 mm, Philips Medical Systems, Cleveland, OH). In addition, all patients underwent an 1.5 Tesla MRI-scan (slice thickness 1.1–4 mm, Ingenia; Philips Medical System, Best, The Netherlands) in treatment position. Imaging details are listed in the online supplement. For each patient, all images were transferred to an in-house developed delineation software tool [9]. The MRI sequences were registered to the planning CT by rigid mutual information registration on a box around the tumor. The attending radiation oncologist contoured the GTV, also referred to as boost (GTVb), and CTV, referred to as elective CTV (CTVe) (Figure 1). The GTVb was defined as the macroscopic (gross) extent of the spinal lesion that is demonstrable on the imaging modalities. The CTVe encompassed the bony compartment containing the GTVb: the entire vertebral body, pedicle, transverse process, lamina, or spinous process was included in the CTV if any of these segments contained the GTVb [10]. Organs at risk (OAR) in close proximity to the tumor were delineated as well. The most important OARs during plan optimization were spinal cord or cauda, nerve roots in which the ipsilateral and contralateral nerve roots were combined a

total nerve root volume, bowel, large vessels, and esophagus. Both the GTVb and the CTVe were expanded with a 2 mm margin (PTVb = GTVb + 2mm; PTVe = CTVe + 2mm). A 2 mm planning OAR volume (PRV) margin was applied to the spinal cord to account for geometrical uncertainties and spinal cord motion variations in location [11, 12]. The same delineations were used for both SIB and non-SIB treatment plans.

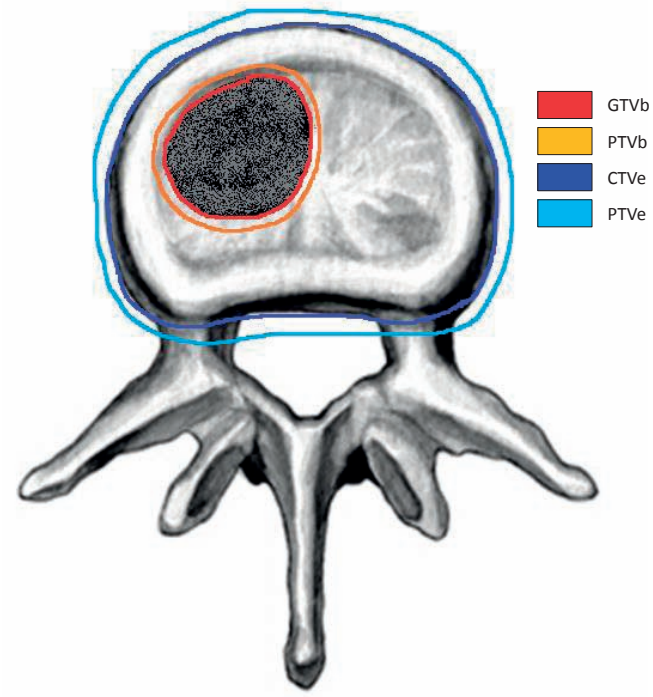

Figure 1. Delineation and planning for representative case 7. (A) Axial plannings CT slice showing the simultaneous integrated boost (SIB) SBRT dose distribution for a small metastasis in the L1 lumbar vertebral body. In this patient, the dose to the elective surrounding relatively healthy bone was effectively reduced from 18.4 Gy to 10.9 Gy. (B) The non-SIB SBRT radiation treatment plan that this patient would have been given without the SIB SBRT approach.

Treatment planning

Volumetric arc therapy treatment (VMAT) plans were created using the Monaco treatment planning system version 5.1 (Elekta, Stockholm, Sweden) which makes use of a Monte Carlo algorithm. The plans were designed for an Elekta Synergy linear accelerator equipped with a 5 mm multileaf collimator (Elekta Inc., Crawley, UK). Two 10 MV photon beam posterior partial arcs with an average arc length of 115° were employed. The maximum number of control points per arc was set to 144, the minimum segment width to 0.5 cm, the collimator angle to 0°, and the Monte Carlo standard deviation per control point to 8%. The calculation grid resolution was 2 x 2 x 2 mm.

Plan optimization

For the SIB treatment plans, doses of 18 Gy to the PTVb and 8 Gy to the PTVe were prescribed in a single fraction. A treatment plan was devised in which 90% of the PTV had to receive at least 90% of the prescribed dose, in accordance with the RTOG 0631 study [13]. To the PTVb, a maximum dose of 25.2 Gy and a mean dose in the range 17–19 Gy was allowed. Treatment plans were optimized according to a priority list which guided the planning process in making compromises between competing constraints and objectives (Table 2). In the non-SIB treatment approach, the entire PTVe was prescribed 18 Gy in a single fraction. A maximum dose of 25.2 Gy and a mean dose in the range of 17–19 Gy was allowed to this volume. Uniformly to the SIB SBRT plans, target coverage was defined as 90% of the PTV had to receive at least 90% of the prescribed dose (V16.2Gy of the PTVe >90%). Treatment plans were optimized according to the priority list (Table 2) substituting PTVe to PTVb without using step 4 and step 6. For both treatment planning strategies, the maximum volume of the spinal cord that was allowed to receive 10 Gy was 0.35 cm^3. Maximum dose permitted to the PRV of the spinal cord was 12.2 Gy. The complete list of OAR dose constraints are available as supplement.

Table 2. Priority list for the optimization of the treatment plans

Priority	Structure	Parameter	Objective or Constraint	Monaco cost function
1	Spinal cord	V_{10Gy}	< 0.35 cm^3 (H)	Serial
	Spinal cord PRV	$D_{2\%}$	< 12.2 Gy (H)	Maximum dose
2	PTV_b	$D_{2\%}$	< 25.2 Gy (H)	Maximum dose
3	PTV_b	D90%	> 16.2 Gy (S)	Target EUD
4	PTV_e	D90%	> 7.2 Gy (S)	Target EUD
5	PTV_b	D_{mean}	17–19 Gy (S)	Quadratic dose
6	PTV_e – PTV_b	-	Steep (S)	Quadratic dose
7	PTV_e + 2 cm		Rapid dose fall-off (S)	Quadratic dose

Abbreviations: D, dose; EUD, equivalent uniform dose; Gy, Gray; H, hard objective or constraint; PRV, planning organ at risk volume; PTVb, planning treatment volume of the GTVb; PTVe, planning treatment volume of the CTVe; S, soft objective or constraint

Plan evaluation and statistical analysis

Dose volume histograms were evaluated for target volume dosimetry and OAR sparing. For each patient and planning modality, median values on target volume coverage and the Paddick conformity index (CI) [14] were calculated. The delivery time of each plan was recorded. The agreement between planned and delivered dose was assessed by the Delta4 diode array phantom (ScandiDos, Uppsala, Sweden) [15, 16]. The measured dose distribution was compared to the planned one, on a volume representing the Delta4 phantom, using the gamma analysis algorithm available in the dosimeter's software in terms of the relative number of diodes (pass rate) which satisfied the (3%, 2mm) gamma criterion with a 95% pass rate tolerance [17]. Paired data was evaluated using the non-parametric Wilcoxon signed-rank test, a P value <0.05 defined statistical significance.

RESULTS

For all 12 cases, a clinically acceptable and deliverable SIB and non-SIB treatment plan was obtained. A representative dose distribution plane for the two planning approaches is shown in figure 2. For SIB SBRT plans, the median V16.2Gy of the PTVb was 95% (range 80–100%) which was higher compared to the median V16.2Gy of the PTVb in the non-SIB SBRT plans (92%, range 75–100%), and this difference was statistically significant (p=0.019) (Table 3). In four of the SIB SBRT cases, the PTVb coverage was below 90% due to the proximity to the spinal cord. For these cases, the median shortest distance between tumor and spinal cord was 0.5 mm. In contrast, the median shortest distance between tumor and spinal cord for cases with a PTVb coverage more than 90% was 2 mm. The median PTVe coverage of the non-SIB SBRT treatment plans (V16.2Gy) was 81% (range, 64–95%).

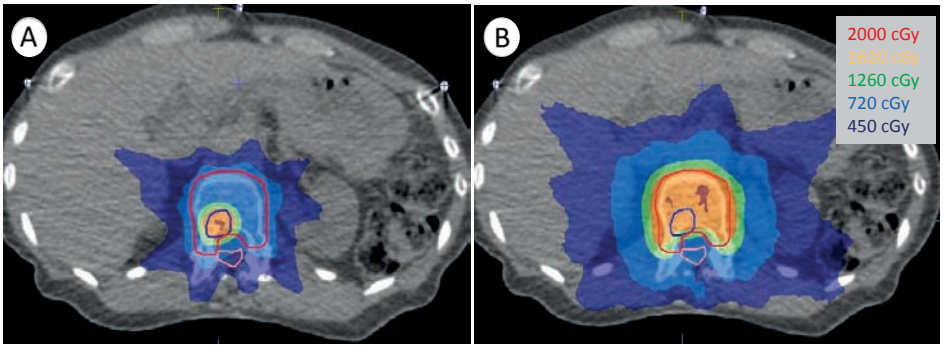

Figure 2. Delineation and planning for representative case 7. (A) Axial plannings CT slice showing the simultaneous integrated boost (SIB) SBRT dose distribution for a small metastasis in the L1 lumbar vertebral body. (B) The non-SIB SBRT radiation treatment plan that this patient would have been given without the SIB SBRT approach. In this patient, the dose to the elective surrounding relatively healthy bone was effectively reduced from 18.4 Gy to 10.9 Gy.

The median PTVb mean dose was 19 Gy (range 18–19 Gy) and 18 Gy (range 17–19 Gy) for SIB and non-SIB SBRT plans, respectively. In SIB SBRT plans, the median mean dose to the (PTVe minus PTVb) volume was 12 Gy (range 10–13 Gy), while this was 17 Gy (range 16–18 Gy) for the non-SIB SBRT plans (p=0.002) (Table 3). The largest difference between the two dose distributions was for case 7 with a reduction of the PTVe mean dose of 8 Gy. In all plans, the D2% near maximum dose (*ie.*, priority 2) was less than 140% of the prescribed dose. For both planning approaches, the spinal cord constraints were always met. The OAR constraints were easier to meet with a SIB SBRT approach with lower maximum doses to important surrounding tissues (Table 3). Nerve roots were better spared using the SIB technique with a reduction of the median maximum dose of 3 Gy. For individual cases, the reduction using the SIB technique was up to 7 Gy.

Table 3. Dosimetric parameters for SIB and non-SIB treatment plans for single dose spinal SBRT

	SIB		Non-SIB		*p*-value
	Median	Range	Median	Range	
Target coverage					
V16.2Gy PTVb (%)	95.3	80.5–100	91.6	75.1–100	0.019
V16.2Gy PTVe (%)	38.9	6.4–60.9	80.6	64.0–95.4	0.002
V7.2Gy PTVe (%)	100	97.1–100	100	100–100	0.043
Target dosimetry					
D2% in PTVb (Gy)	20.5	19.2–24.1	–	–	–
D2% in PTVe (Gy)	–	–	20.1	19.7–22.55	–
D2% in (PTVe-PTVb) (Gy)	17.3	16.1–18.1	–	–	–
Dmean PTVb (Gy)	18.7	17.5–19.0	17.9	17.2–19.0	0.015
Dmean PTVe (Gy)	14.5	10.6–16.5	17.6	16.4–18.4	0.002
Dmean (PTVe-PTVb) (Gy)	11.9	10.1–13.2	17.4	16.0–18.4	0.002
Conformity index* PTV_b	0.6	0.4–0.9	0.3	0.0–0.5	0.003
OAR evaluation †					
D1cc Spinal cord PRV (Gy)	7.7	5.5–9.1	9.5	7.6–9.6	0.018
V10Gy Spinal cord (cc)	0.0	0.0–0.28	0.27	0.02–0.35	0.018
D1cc Cauda equina (Gy)	10.8	8.3–12.8	12.4	11.7–13.1	0.068
V13Gy Cauda equina (cc)	0.1	0.0–0.6	0.5	0.11–2.0	0.138
D0.1cc Nerve roots (Gy)	14.4	9.2–17.6	17.2	15.7–17.6	0.037
D1cc Bowel (cc)	8.8	4.5–13.7	10.7	5.1–13.5	0.046
V11.2Gy Bowel (cc)	0.2	0.0–4.3	1.4	0.0–4.8	0.114
D1cc Large vessels (Gy)	10.6	4.7–14.5	14.1	7.5–15.1	0.012
V12Gy Large vessels (cc)	0.3	0.0–2.67	3.3	0.0–4.6	0.012
D1cc Esophagus (Gy)	8.1	6.2–11.9	11.5	6.7–12.1	0.080
V11.9Gy Esophagus (cc)	0.0	0.0–1.1	0.6	0.0–1.2	0.273
Delivery time (s)	723	635–883	858	649–1326	0.013
Monitor units	5757	4981–7244	6826	5072–10654	0.013

*The Conformity index for the PTVb is calculated according to the formula of Paddick [14]
†Based on treatment plans with target volume near OAR
Abbreviations: D, dose; D2% = maximum dose in Gy to 2% of the volume; Dxcc = maximum dose in Gy to *x* cc of the volume; OAR, organ at risk; PTVb, planning treatment volume of the GTVb; PTVe, planning treatment volume of the CTVe; SIB, simultaneous integrated boost; V, volume; V*x*Gy = volume in cc or percentages receiving at least *x* Gy.

The median delivery time of the non –SIB SBRT plans was 2 minutes longer than the delivery times recorded for the SIB plans (p=0.013) (Table 3). Measured dose distributions showed excellent agreement with the calculated ones for all the plans and planning approach, with on average 99% of the overall area within the region of interest fulfilling the acceptance criterion.

DISCUSSION

A comparative planning study on single fraction spine SBRT was performed to evaluate the dosimetric feasibility of SIB SBRT treatment planning approach for spinal metastatic disease. Both the SIB and non-SIB VMAT treatment approach resulted in clinically acceptable and deliverable treatment plans. Successful (non-)SIB treatment plans that fulfilled the prescription were obtained except in cases where the PTVb or PTVe was lying in close (*ie,* 0.5 mm) proximity of the spinal cord. For spinal metastases, a trade-off has to be made between dose limiting to critical structures and PTV coverage [18]. In cases where the tumor is adjacent to the spinal cord, PTV coverage is harder to achieve. Despite not fulfilling the prescription dose in all cases, the objective on the mean dose in PTVb was always met assuring sufficient high dose to the metastasis itself, both for the SIB as for the non-SIB SBRT plans. In the SIB SBRT treatment plans, the CTVe was better spared from the high dose prescribed to the spinal metastases. The mean dose in the PTVe was considerably lower compared to the dose to the PTVe in the non-SIB plans resulting in a lower dose to the relatively healthy surrounding bone. Our planning study shows that a dose reduction up to 8 Gy is achievable. Extrapolating the dose-response curve provided by Sahgal *et al.*[4], by sparing the relative healthy surrounding bone structures by on average 5.5 Gy, it allows reducing the number of VCF with 50% (*ie,* from 10% to 5%).

It was hypothesized that late radiation effects in the form of bone and tumor necrosis compromises the ability of the vertebrae to withstand the axial loading forces, leading to an increased risk of the occurrence of VCF [3, 4]. This process might be comparable to the risk of tissue necrosis in brain radiosurgery, with the risk of necrosis increasing with a higher dose per fraction [19]. A clinicopathologic analysis provided histopathological evidence to support this hypothesis in two cases [20]. This case report explored the potential mechanism underlying SBRT-induced VCF by describing two patients who were treated with spine SRBT. These patients subsequently developed signal changes on MRI consistent with tumor progression and VCF. However, biopsy showed radiation-induced osteoradionecrosis which was likely a causative factor in destabilizing the vertebrae that resulted in the observed VCFs [20]. More support for this hypothesis is provided by studies determining the VCF risk in patients receiving high dose radiation for primary tumors in the thoracic or abdominal region. Especially in high risk patients, vertebral fractures are associated with the absorbed radiation dose in which fractures are mostly seen in the high dose regions [21].

Several authors reported on some sort of dose escalation within the GTV for spinal SBRT. Lee *et al.* showed in five patients that deliverable plans can be obtained for spine metastases using a SIB approach. They compared step-and-shoot intensity modulated radiotherapy (IMRT) and VMAT techniques concluding that both techniques can deliver the concomitant hypofractionated (5 fractions) dose regime to the visible metastasis [22]. In the clinical study of Lubgan *et al.*, SIB plans for spinal SBRT were shown to be feasible while keeping the incidence of side effects low: they reported one VCF after four months in 33 patients. However, in their study the prescribed dose difference between PTVb and PTVe was 0.75 Gy per fraction with respect to the 10 Gy of this work [23]. Also at MD Anderson Cancer Center the SBRT planning protocol for spinal metastases includes a SIB technique for single fraction SBRT: 18-24 Gy is prescribed to the GTV, while the CTV receives 16 Gy [24]. Follow-up data from patients treated at MD Anderson Cancer Center showed a VCF in 32 (41%) out of 79 patients, still indicating high VCF rates after single fraction SBRT with a SIB approach [7]. However, less than half of the included patients in this report actually received SBRT with a SIB approach. Moreover, with an elective dose of 16 Gy the dose to the CTV is still relatively high. Finally, Mantel *et al.* reported on safety of fractionated SBRT using a SIB concept in 26 out of a total of 36 patients. Seven patients (22%) developed progressive VCF, however, all vertebrae without a VCF prior to SBRT remained fracture free [25].

Beside the potential mitigated risk of SBRT-induced VCF, the SIB SBRT treatment planning approach has more possible advantages over non-SIB SBRT plans. With regard to the surrounding tissues, important OAR are better spared using a SIB SBRT strategy. Especially the (maximum) dose to the spinal nerve roots is significantly lower in SIB SBRT plans possibly lowering the risk of radiculopathy [26]. Bowel and large vessels were also better spared potentially reducing side effects. Furthermore, excluding patient positioning and image guidance, the median delivery time of SIB plans was found to be 2 minutes shorter compared to the non-SIB plans. A shorter delivery time might result in less intrafraction motion and increase of patient comfort. Finally, current consensus guidelines recommend to delineate GTV as the complete extent of the gross metastatic tumor using all available clinical information and imaging modalities [10]. Following these guidelines, an homogenous dose distribution is delivered to the CTV. However, we found that by optimizing the non-SIB SBRT treatment plans for PTVe coverage, the dose to the metastasis itself was lower compared to SIB SBRT plans. Therefore, also in non-SIB SBRT planning, the GTV might be considered as well in plan optimization.

In all patients, MRI guidance was used to delineate GTV and organs at risk in addition to CT. High quality multimodal imaging is a key component in (spinal) SBRT since very conformal dose distributions intended to target the tumor necessitates accurate localization and visualization of the latter. Several imaging strategies have been described, however, it is common practice today to register a planning or diagnostic MRI scan with the planning CT scan for the treatment of

spinal metastases [27, 28]. Especially in a SIB approach, optimal MRI scans are imperative, since the GTV forms the target rather than a clinically defined volume such as the entire vertebral body. In an extensive meta-analysis by Yang *et al.*, MRI was found to have the highest sensitivity on both a per-patient and per-lesion basis compared to PET, CT, or bone scintigraphy [29].

A limitation of our study could be the reproducibility of the study observations since treatment plans are operator dependent. Moreover, these observations are dependent on choice of optimization parameters and dose calculation algorithm. In our department, the treatment planning radiotherapists work with an priority list which should allow getting more consistent plans with respect to target coverage and conformity [30]. Furthermore, we need follow-up data of patients who are treated with a SIB SBRT approach to confirm the hypothesis of less toxicity by sparing the surrounding relatively healthy bone. In the VERTICAL trial, patients with bone metastases are treated using stereotactic SIB plans [31]. Their follow-up data will be used to explore whether using a SIB might reduce the number of VCF.

In conclusion, the required plan quality and accuracy in dose delivery can be achieved using a SIB SBRT treatment planning approach for spinal SBRT. Compared to non-SIB SBRT treatment plans, a substantial reduction of the dose to the relatively healthy bony compartment is achieved. This might mitigate the risk of radiation induced vertebral fractures. Clinical prospective trials with sufficient follow-up are needed to confirm this hypothesis.

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APPENDICES

Appendix 1: Details of CT and MRI scans

CT imaging was performed prior to radiation treatment and in radiotherapy position on a Philips large bore CT Scanner (Philips Medical Systems, Cleveland, OH). All CT planning scans were acquired with 1-mm slice thickness. Patients were laying on an individual evacuated cushion (BlueBAG™, Elekta, Stockholm, Sweden) for comfort during CT-imaging. In addition, when patients are laying in an individual evacuated cushion, we are able to correct for rotations.

In addition, five patients underwent an 1.5 Tesla MRI-scan (Achieva; Philips Medical System, Best, The Netherlands) in the same fixation device as used for CT-imaging. We obtained T1-weighted images in transversal and sagittal directions, including a transversal mDIXON scan, T2-weighted images in transversal and sagittal directions, and diffusion weighed imaging (DWI). The MRI sequences were registered to the planning CT by rigid mutual information registration on a box around the tumor. Details can be found in supplementary Table 1.

Supplementary Table S1. MR imaging parameters

	MR sequences					
	tT1TSE	sT1TSE	tT1TSE	sT2TSE	DWI	tT1FFE
Sequence	Fast spin echo	Fast spin echo	Fast spin echo	Fast spin echo	Single shot spin-echo echo-planar imaging	3D spoiled gradient echo
Contrast	T1	T1	T2	T2	Diffusion	T1
Direction	Transverse	Saggital	Transverse	Sagittal	Transverse	Transverse
Fat suppression	-	-	Multi echo dixon	Multi echo dixon	SPIR	Multi echo dixon
TR/TE (ms)	623/16	658/8	2147/80	4105/80	4367/67	5.7/2.3
Echo train length	8	5	18	18	59	200
B-values (s/mm^2)	-	-	-	-	0/200/800	-
Field of view (mm)	300 x 420	160x 352	300 x 201	350x 199	420 x 300	4530x 400
Acquisition matrix (mm^2)	420 x 406	440 x 337	269 x 376	352 x 348	163 x 165	412 x 412
Slice thickness (mm)	4	4	4	4	4	1.1
Number of slices	25	25	25	50	25	273
Acceleration factor	2.9	1	1	1	2	3.4
Number of averages	2	2	4	2	3/5/7	2
Acquisition time (s)	127	181	360	378	179	304

MR imaging parameters and MRI sequences. cT1w: coronal T1 weighted image, sT1w: sagittal T1 weighted image, tT1w: transverse T1 weighted image, T2w: T2 weighted images. TE : echo time, TR: repetition time.

Supplementary Table S2. Constraints of organs at risk

Organ	Contraint
Bladder	Max 22 Gy, V8.7Gy <15cc
Bowel bag (including rectum)	Max 16 Gy, V11.2Gy <5cc
Brachial plexus	Max 16 Gy, V14Gy <3cc
Brain	Max 15 Gy, V12Gy <3cc
Brain stem	Max 15 Gy, V10Gy <1cc
Bulbus oculi	V14Gy <3cc
Cauda	Max 14 Gy, V13Gy <5cc
Cochlea	Max 12 Gy
Esophagus	Max 14 Gy, V11.9 <5cc
Heart	Max 22 Gy, V16Gy <15cc
Kidneys	V5Gy <25%
Large vessels	Max 18 Gy, V12Gy <5cc
Larynx	V10.5Gy <4cc
Liver	V9.1Gy <700 cc
Lung	V7Gy <750cc
Main bronchus	Max 18 Gy, V12Gy <5cc
Nerve roots	Max 18 Gy*
Optic chiasm	Max 12 Gy
Optic nerve	Max 10 Gy
Renal hilum	V10.6Gy <33%
Retina	Max 5 Gy
Skin	Max 16 Gy, V14.4Gy <10cc
Spinal cord	Max 12 Gy, V10Gy <0.35cc
Spinal cord, PRV	Max 12.2 Gy
Stomach	Max 12 Gy, V11.2Gy <10cc
Trachea	Max 18 Gy, V10.5Gy <4cc
Urethra	Max 12 Gy, V10Gy <1cc

*This constraint was added in response to the results of this planning study.
Abbreviations: Gy, Gray; max, maximum; V, volume

CHAPTER 7

Impact of stereotactic body radiotherapy on pain and local control for bone metastases: A systematic review and meta-analysis

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ABSTRACT

Importance

Stereotactic body radiotherapy (SBRT) might improve pain and local control in patients with bone metastases. An estimate of pain response and local control rate is yet unknown.

Objective

To determine pain and local control rate following SBRT for bone metastases.

Data sources

Pubmed, Embase, and Cochrane databases were systematically reviewed with librarian guidance to identify studies published from inception to April 14, 2017.

Study Selection

In total, 2619 unique studies of patients with bone metastases from solid tumors who underwent SBRT in 1–6 fractions, with or without a prior history of radiotherapy or surgery were screened. Two authors independently analyzed the studies for inclusion.

Data Extraction and Synthesis

Following the MOOSE and PRISMA guidelines, data were extracted from text and tables of articles independently by two investigators who were blinded to each other's results. Study quality was assessed by pre-defined criteria. Pooled response rates and 95% confidence intervals (95% CI) were estimated using a random effects model.

Main Outcomes and Measures

Pain response, expressed as the proportion of patients experiencing pain relief; and local control, expressed as the proportion of lesions without local failure on follow-up imaging.

Results

In the systematic review, 57 studies (3575 patients) were included. Twenty-nine studies (1865 patients or lesions) were included in the meta-analysis for pain response; 40 studies (3705 lesions) for local control. Pooled pain response was 81% (95% CI 76–86%). Pain response was highest in studies reporting pain response of assessable lesions (85%). Whether opioid use was accounted for in the response evaluation, was of largest influence (response rates of 74% in studies accounting for opioid use *vs.* 82% in non-accounting studies). Pooled local control rate was 86% (95% CI 82–89%). Local control was highest in studies using single fraction SBRT (93%) compared to studies applying multiple fractions (86%).

Conclusions and Relevance

SBRT for bone metastases seems associated with higher rates of pain relief than are reported following conventional radiotherapy, and local control rates seems high as well. These improved outcomes may, however, reflect patient selection and non-standard outcome assessments. This observation needs to be assessed in large randomized trials.

INTRODUCTION

Patients with advanced cancer commonly present with pain, with bone metastases being the most frequent cause of cancer-related pain [1, 2]. Conventional radiotherapy is the cornerstone of the management of bone metastases. Approximately 60% of patients will experience a reduction in pain following conventional radiotherapy with 25% having complete resolution at the treated site [3, 4]. The mean duration of palliation is approximately four months [5] with a net pain relief of 68–71% [6]. To date, no dose-response effect has been demonstrated as several randomized trials have shown that a single 8 Gy dose provides equivalent pain control to more fractionated regimens of 20–30 Gy [3, 4]. Conventional hypo-fractionated palliative radiotherapy is routinely delivered using two parallel opposed fields or single fields with the dose constrained by organs at risk. Recent advances in the conformality of image-guided radiotherapy techniques, such as stereotactic body radiotherapy (SBRT) or radiosurgery, have enabled the delivery of potentially ablative radiation doses while respecting healthy tissue constraints. Although radiosurgery is commonly used for small volume brain metastases [7], its role in bone metastases remains under investigation. It is hypothesized that the delivery of ablative doses to bone metastases is able to improve rates of both pain control and local control [8]. Several reviews have been published reporting on the feasibility and efficacy of SBRT for bone metastases [8–11]. To the best or our knowledge, however, none of these reviews derived pooled estimations of relevant clinical outcomes. Furthermore, these reviews were not conducted according to the MOOSE and PRISMA guidelines [12, 13]. Our study, therefore, aims to carry out a systematic review and meta-analysis to quantify pain response and local control following SBRT for bone metastases. We furthermore summarized the evidence on toxicity and quality of life following SBRT for bone metastases.

MATERIAL AND METHODS

This systematic review was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [13] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist [12]. The protocol for this review was published in the PROSPERO international prospective register of systematic reviews [14].

Search strategy

A structured search was conducted in PubMed, Embase, and Cochrane electronic databases on March 16th 2016. The search was updated on April 14th, 2017. Search terms included synonyms for ‘bone metastases’ and ‘stereotactic body radiotherapy’, which were combined and searched in title and abstract (Appendix A1). No search limits were used. Reference lists from included articles were cross checked to identify additional articles.

Study selection

All studies were independently assessed by two authors (JMV, EW, or KS) for eligibility. All studies in patients with bone metastases from solid tumors who underwent SBRT in 1–6 fractions, with or without a prior history of radiotherapy or surgery were included. Original studies in English with full text available were included. All study designs were accepted. If eligibility for inclusion in the review could not be determined based on title and abstract, the full text was reviewed.

To qualify for inclusion in the meta-analysis, outcomes had to be reported on a patient level, primary outcomes had to be known for at least 40% of the population, and the size of the study population had to be 10 or more. Where individual patients were included in multiple published series, the most complete or recent article was cited [15]. If less than 10 patients overlapped, both study populations were included. In series comparing SBRT with conventional radiotherapy, only the data for the SBRT cohort were included.

Data extraction and quality assessment

The primary endpoints were pain response and local control rate. Pain response rate was expressed as the proportion of patients experiencing pain response according to the definition used in the original study. For every study, it was recorded whether the response was reported on a patient or lesion level. If available, the proportion of responders was recorded or calculated for assessable patients (*ie,* patients with follow-up data available) and for the total treated population (*ie,* all patients originally included in the study regardless of availability of follow-up data). If only the proportion of responding patients was reported without exact numbers, the response was regarded as for assessable patients. Local control rates were expressed as the proportion of lesions without local failure on diagnostic follow-up imaging, according to the definition used in the original study. If available, the proportion of locally controlled lesions was recorded for both the assessable and total treated population. Secondary endpoints were duration of pain relief, toxicity according to the CTCAE [16] and quality of life. Vertebral compression fractures were not taken into account as this is covered elsewhere [17]. In addition, we extracted study design, study population, demographics, primary tumor, localization of metastases, dose and fractionation schedule, follow-up time, measurements of outcome, and technical aspects of the stereotactic treatment. As most studies reported the Karnofsky performance score (KPS), if performance status was reported as WHO or Zubrod performance status it was converted to the KPS [18]. All data were extracted by two authors (JMV, KS) independently directly from the text or calculated independently using available information. Study authors were contacted for additional data if information was missing. Study quality was assessed by pre-defined criteria based on items listed in the STROBE statement [19] and items relevant for bone metastases research specifically.

Statistical analysis

The R statistical environment (version 3.4.0, R Development Core Team, 2011) with metafor package was used for statistical analysis [20]. To generate the risk of bias graph, Review Manager (version 5.3) was used [21]. Potential publication bias was assessed visually by generating funnel plots [22]. For each study, pain response and local control rate were logit transformed and pooled. The back-transformed pooled values were presented as proportions with 95% confidence interval (95% CI). Random effects models, using a restricted maximum likelihood estimator, were used to calculate a pooled estimate regardless of the I^2 measure of heterogeneity. Pain response and local control were estimated by pooling all studies reporting on these outcomes. Additionally, pain response was pooled in studies reporting pain on a patient level and on a lesion level, both further subdivided for the assessable patients/lesions and the total treated population. Local control rate was estimated by pooling studies reporting local control for the assessable as well as for the total treated population. For both pain response and local control, sensitivity analyses were performed, evaluating the impact of primary tumor, fractionation schedules, data collection (*ie,* prospective *vs.* retrospective, patient reported outcomes), taking opioid use into account, and follow-up (*ie,* at least 1 year and at least 80%).

RESULTS

The search yielded 2619 unique articles. After screening of these articles on title and abstract, 343 studies were screened on full text, of which 290 were excluded (Figure 1). Most of the excluded articles were conference proceedings, reported duplicate data, or did not report outcomes for bone metastases separately. One additional article was included after cross-referencing [23] since it used 'high dose' instead of 'stereotactic radiotherapy' in its title. The search update yielded five more articles [23–28], of which two articles provided updated information about already included studies replacing the earlier included studies [23, 29]. Finally, 57 studies were included in the review (3575 patients), 29 studies entered the meta-analysis for pain response (1865 patients), and 40 studies were used for local control (3521 patients). The funnel plots showed some asymmetry, indicating publication bias for pain response and local control (see Appendix figures A1 and A2).

Study description and quality assessment

Most studies had a clear description of the study population (82%) and the SBRT procedure (70%) (Figure 2, Appendix tables A1 and A2). A clear definition of the outcome and whether the outcome was measured on standard and regular time points during follow-up was provided in around 50% of the studies (Figure 2, Appendix tables A1 and A2). Almost 60% of the included studies did not report how many patients were lost to follow-up or had more than 80% attrition (Figure 2, Appendix tables A1 and A2).

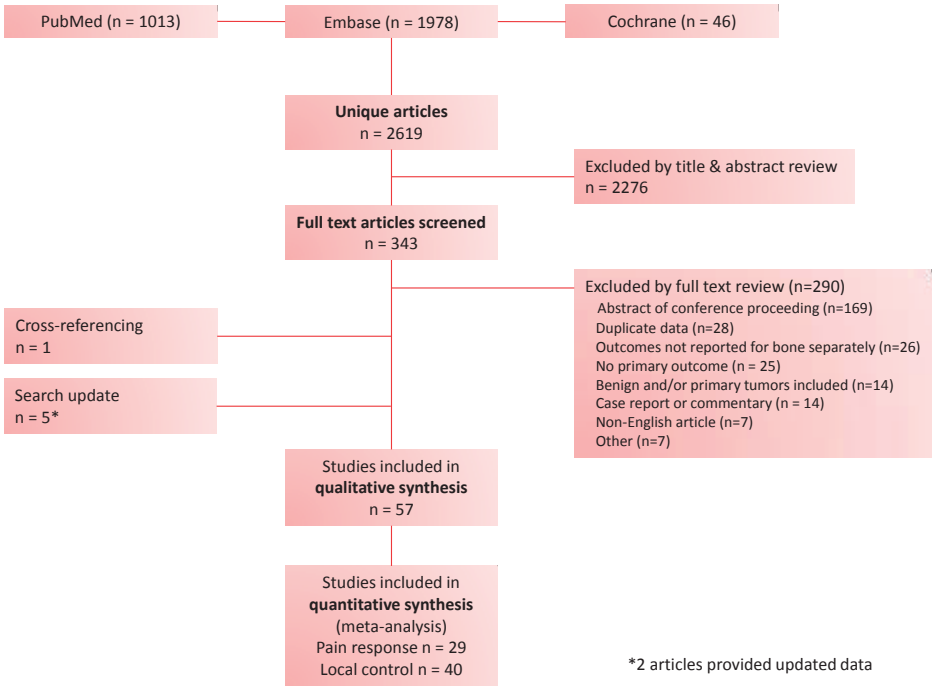

Figure 1. Flow chart of systematic search

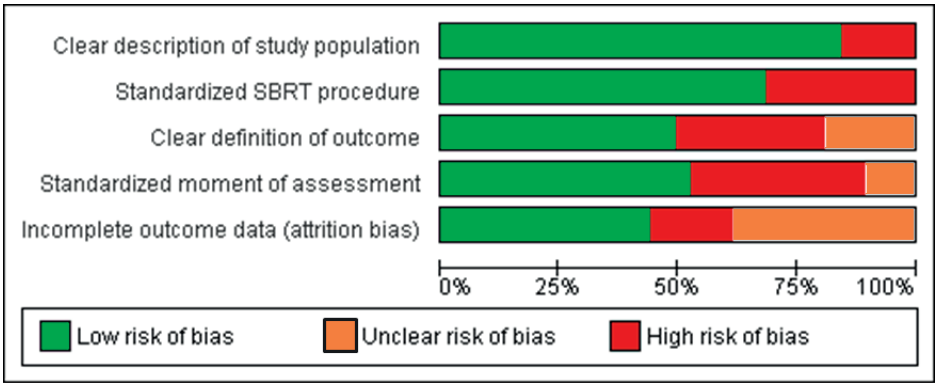

Figure 2. Graphical representation of quality appraisal item presented as percentages across all included studies. Studies with a clear description of the study population reported how many patients received postoperative SBRT or re-irradiation. Studies reporting at least report on immobilization, imaging used for contouring, applied PTV margins, and dosimetric parameters such as coverage or conformity index were regarded using standardized SBRT procedures. Studies with a clear definition and standardized moment of outcome assessment for pain response but not for local control or vice versa, were regarded unclear. High risk of attrition bias was considered less than 80% complete follow-up data.

All studies were prospective or retrospective single or multicenter cohort studies, except for the study by Berwouts *et al.* [30] who randomized 45 patients into three different treatment arms (Appendix table A1). Median age ranged between 52 and 68 years. Performance status was reported in 28 of the 57 studies and the mean KPS varied from 75% to 95%. Median survival ranged from 8 to 47 months [31–33]. Most studies included patients with bone metastases from a mixture of solid tumors. Twelve studies selected patients based on primary tumor site, including renal cell carcinoma, hepatocellular carcinoma, melanoma, breast, and prostate cancer (Appendix table A1 and A2). All but eight studies included patients with spinal metastases only (Appendix tables A1 and A2). Stereotactic dose schedules were standardized in 40 of 57 studies reporting a reproducible treatment protocol, with dose schedules ranging from 6 Gy to 52.5 Gy in 1-6 fractions (Appendix tables A1 and A2). Treatment volumes were defined in 39 studies in which the treatment planning margins varied from 0 to 5 mm. A simultaneous integrated boost (SIB) approach was used in four studies [34–37].

Of the 38 articles describing pain control, only four articles [30, 32, 37, 38] used the recommended international consensus standard of reporting pain response on an 11-point ordinal scale accounting for pain medication[39, 40]. Twenty-four studies did not include a (clear) definition of pain response (Appendix table A1). Nine studies used a non-standard definition of pain control, such as a pain score reduction of at least 50% [35, 41–48]. The definition for pain control in the RTOG 0631 protocol, requiring a reduction of at least 3 points on a 11-point rating scale without increase in narcotic pain medication [49], was used in two studies [50, 51]. For the calculation of response, time of assessment was standardized at 1-3 month after treatment in 13 studies (Appendix table A1). The remaining studies did not use a standardized time interval from SBRT to response assessment, so it was assumed any response during follow-up was included.

For assessment of local control, 17 of the 45 studies evaluating local control used frequent follow-up (mostly three monthly) MRI imaging (Appendix table A2). The modality on which local control was assessed was not reported in 14 studies (Appendix table A2). In most studies, local control was defined as the absence of tumor growth indicating stable disease (n= 19), whereas some studies also accounted for pseudo-progression (*ie,* when changes occur soon after SBRT [52]) [24, 53, 54]. The definition of local control was not given in 14 studies (Appendix table A2).

Pain response

Twenty-nine studies met the criteria for inclusion in the meta-analysis on pain response with an overall pooled estimate of response of 81% (95% CI 0.76–0.86) (Figure 3). Heterogeneity was high (I^2 =80%). The pooled estimate of pain response for assessable patients was 77% (95% CI 0.67–0.84) (Table 1). For the total treated population, the pooled pain response was 71% (95% CI 0.56–0.82). The pooled estimates for assessable lesions and total treated lesions were higher: 85% (95% CI 0.79–0.89) and 72% (95% CI 0.62–0.80) respectively (Table 1). Pain response per-

centages in retrospective studies were higher compared to reported pain response in prospective studies (82% *vs.* 78% respectively, Table 1). Also, studies that evaluated pain response without taking narcotic use into account reported higher pain control rates compared with studies taking narcotic use into account (85% *vs.* 74% respectively, Table 1). The difference in pain response between studies using patient reported outcomes and studies using physician reported outcomes was small (79% *vs.* 82% respectively, Table 1). Pain response in studies reporting multiple fraction SBRT only was lower than in those including only single fraction treatments or mixed single and multiple fraction cohorts (Table 1).

Four studies reported on the duration of response. In a retrospective study, Hunter *et al.* 2012 [50] compared 8–16 Gy single fraction SBRT with conventional radiotherapy (8–30 Gy in 1–10 fractions) in 76 patients with spinal lesions. For patients who responded (62%), median duration of response was significantly longer in patients who had received SBRT (4.8 months) compared to 1.7 months after conventional RT. Lee *et al.* showed a median duration of pain relief of 3.2 months after SBRT in 57 patients with spinal metastases [43]. A small study including 18 RCC patients with bone metastases found that 32% of patients who responded had a symptomatic recurrence after a mean of 10 weeks [55]. In contrast, a much longer median duration of pain relief of 13.6 months was reported by Ryu *et al.* in 49 patients with a single isolated spinal metastasis [47].

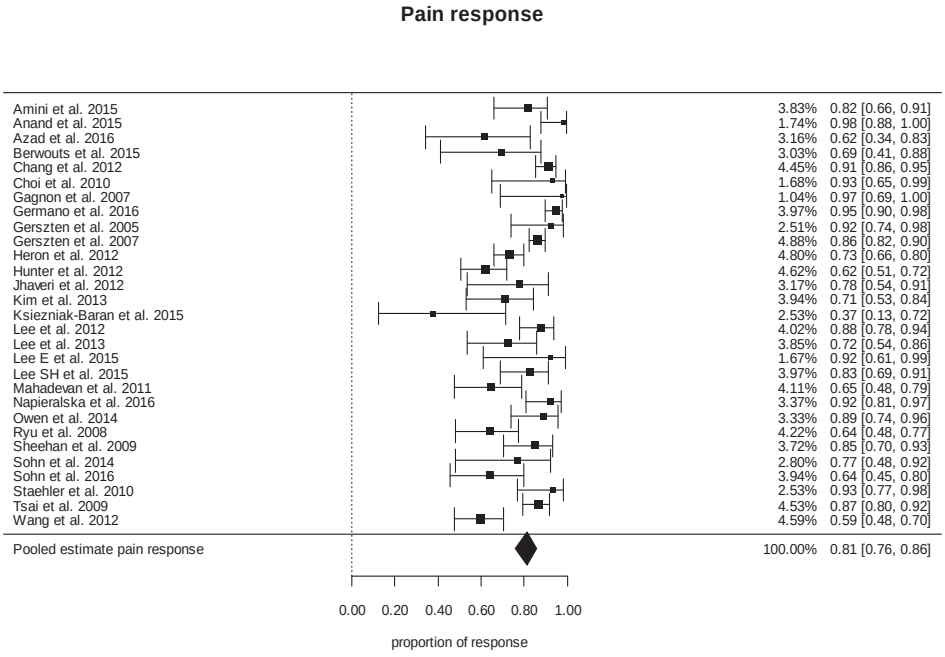

Figure 3. Meta-analysis of studies evaluating pain response after SBRT for bone metastases; values in parentheses are 95% confidence intervals

Table 1. Summary of overall pooled estimates, including the stratified analyses and sensitivity analyses for pain relief

Outcomes	Number of studies	Total number of patients	Pooled effect estimate	95% CI	Comments
Overall effect	29	1865	81%	76-86%	Regardless of level or population
Assessable population					
Per patient	16	561	77%	67-84%	
Per lesion	14	1186	85%	79-89%	
Total treated population					
Per patient	14	545	71%	56-82%	
Per lesion	7	405	72%	62-80%	
Fractination schedule					
Single fraction	7	655	83%	70-92%	Effect in assessable patients/lesions
Both SF and MF	14	523	81%	72-88%	Effect in assessable patients/lesions
Multiple fractions	7	373	74%	65-81%	Effect in assessable patients/lesions
Data collection					
Prospective	6	519	78%	64-88%	Effect in assessable patients/lesions
Retrospective	23	1189	82%	76-87%	Effect in assessable patients/lesions
Use of PROMs					
Yes	12	918	79%	72-85%	Effect in assessable patients/lesions
No	17	947	82%	74-89%	Effect in assessable patients/lesions
Accounting for opioid use					
Yes	10	683	74%	66-81%	Effect in assessable patients/lesions
No	19	1025	85%	78-90%	Effect in assessable patients/lesions
Primary tumor					
Mixed	21	1619	80%	73-86%	Effect in assessable patients/lesions
Renal cell carcinoma	4	136	82%	73-89%	Effect in assessable patients/lesions
HCC	2	42	78%	38-96%	Effect in assessable patients/lesions
Breast cancer	1	18	100%	NC	Effect in assessable lesions
Prostate cancer	1	51	92%	81-97%	Effect in assessable patients

Abbreviations: HCC, hepatocellular carcinoma; MF, multiple fractions; NC, not calculable; PROMs, patient-reported outcome measures; SF, single fraction

Local control

Forty studies were included in the meta-analysis on local control with an overall estimated local control rate of 86% (95% CI 0.82–0.89) (Figure 4). Heterogeneity of the included studies was high (I^2 =83%). The pooled local control rate for assessable lesions was 86% (95% CI 0.83–0.89). Sohn *et al.* [32] included only patients with bone metastases from hepatocellular carcinoma and is a clear outlier with local control rates of only 25%. The exclusion of this study did not change the pooled response (87%). For the total treated population, 23 studies contributed to the pooled estimate of 73% (95% CI 0.63–0.81). Sensitivity analyses looking at local control rate in studies

with more than 12 months of follow-up or with at least 80% follow-up did not show large differences (86% for both analyses, Table 2). Studies that included patients with spinal cord compression showed a slightly lower local control rate compared with studies that excluded those patients (84% *vs.* 88%, Table 2). Studies that treated patients with a single fraction reported higher local control rates compared to studies delivering multiple fractions (Table 2).

Toxicity

Overall, 40 of the 57 studies reported on toxicity, which was generally mild and transient. Of the 28 studies evaluating toxicity retrospectively, five grade 3 or 4 toxicities (0.002%) were observed in 2033 patients [25, 27, 28, 31–33, 35, 38, 41, 51, 54–71]. Ten studies including 676 patients recorded toxicity prospectively and reported grade 3 or 4 toxicity in 19 patients (0.03%) [34, 36, 37, 48, 72–77]. The largest prospective study analyzed toxicity in 149 patients using patient reported outcomes, and documented mostly mild toxic effects such as grade 1 and 2 transient numbness and tingling, nausea and vomiting [48]. The twelve grade 3 toxicities were predominantly pain and gastro-intestinal complaints [48]. All other grade 3–4 toxicities were reported in the prospective studies, and were al treatment-related neurologic toxicity [34, 36, 73, 74].

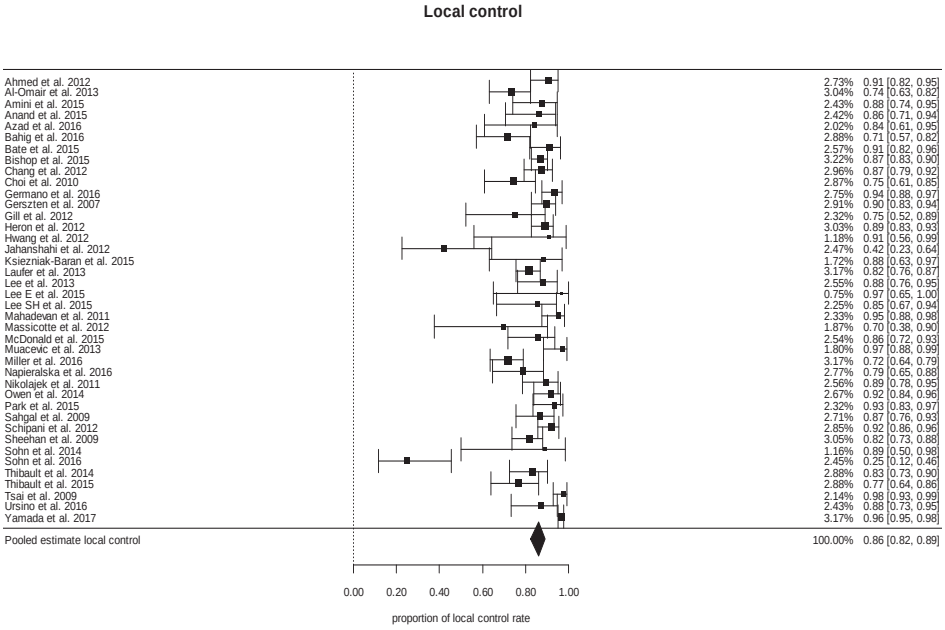

Figure 4. Meta-analysis of studies evaluating local control after SBRT for bone metastases; values in parentheses are 95% confidence intervals

Table 2. Summary of overall pooled estimates, including the stratified analyses and sensitivity analyses for local control

Outcomes	Number of studies	Total number of patients	Pooled effect estimate	95% CI	Comments
Overall effect	40	3600	86%	82-89%	Regardless of level or population
Population					
Assessable	39	3581	86%	83-89%	
Total treated	23	2270	73%	63-81%	
Fractination schedule					
Single fraction	5	1153	93%	89-96%	Effect in assessable lesions
Both SF and MF	27	1941	85%	80-88%	Effect in assessable lesions
Multiple fractions	6	378	86%	79-91%	Effect in assessable lesions
Median follow-up					
At least 1 year	17	2109	86%	81-90%	Effect in assessable lesions
Less than 1 year	22	1463	87%	82-91%	Effect in assessable lesions
Attrition during follow-up					
At least 80%	18	1885	86%	81-90%	Effect in assessable lesions
Less than 80%	21	1696	87%	82-91%	Effect in assessable lesions
Spinal cord compression					
Yes	16	1116	84%	80-88%	Effect in assessable lesions
No	23	2465	88%	83-91%	Effect in assessable lesions
Primary tumor					
Mixed	31	3422	82%	76-87%	Effect in assessable lesions
Renal cell carcinoma	4	253	80%	70-87%	Effect in assessable lesions
HCC	2	39	71%	2-100%	Effect in assessable lesions
Prostate cancer	2	111	89%	43-99%	Effect in assessable lesions
Melanoma	1	19	100%	NC	Effect in assessable lesions (n=8)

Abbreviations: HCC, hepatocellular carcinoma; MF, multiple fractions; NC, not calculable; PROMs, patient-reported outcome measures; SF, single fraction

Quality of Life

Three studies measured quality of life, all using different scales. In the study of Ahmed *et al.*, including 66 patients, 3 month follow-up was available for 15 patients [34]. After SBRT for spinal metastases, improvement was noted on the emotional subscale of the FACT-G questionnaire with an increase from 15.7 at baseline to 18.2 after three months, indicating a clinically meaningful response [78]. Wang *et al.*, using the MD Anderson Symptom Inventory (MDASI [79]) and SF-12 [80] questionnaires, showed no significant change over time for physical or mental health component scores, but scores for disturbed sleep, drowsiness, sadness, fatigue, distress, lack of appetite, nausea, and difficulty remembering were significantly improved at six months follow-up. They also showed that patients whose lesions were categorized as progressive reported significantly more severe pain, fatigue, and drowsiness on the MDASI symptom score

than did patients with stable or smaller lesions [48]. In the small randomized study, Berwouts *et al.* did not find significant differences in QLQ-C15-PAL [81] and QLQ-BM22 [82] at baseline or 1 month between patients treated with an 8 or 16 Gy single fraction [30].

DISCUSSION

This systematic review and meta-analysis looked at the effectiveness of SBRT for bone metastases in patients with advanced cancer, and showed pain response rates of 71–85% and local control rates of 73–86% with associated low toxicity rates. The wide ranges are likely to reflect differing study populations, outcome measurements, and reporting. Excluding the patients for whom no response outcome was measured, increased the percentage of responders. For pain response specifically, focusing on the treated lesion leads to higher pain response rates since overall pain response is influenced by other (non-treated) painful lesions. Overall, pain response rate seems substantially better after SBRT when compared to conventional radiotherapy [3, 4, 6]. Also, radiological local control rates seem excellent [91]. We must, however, be critical in interpreting these data as a number of aspects may give rise to biased estimates of outcomes.

Most importantly, the median survival of patients included in these studies was significantly higher than that of individuals randomized in previous conventional radiotherapy trials or the non-trial population. The median survival in patients with bone metastases treated in previously conducted conventional radiotherapy trials was 7 months [92] and in routine practice has been reported to be even lower (4.8 months) [93]. In comparison, patients in the SBRT studies included here had a median survival of 8 to 47 months. It has been previously demonstrated that patients with survival of over 1 year following treatment have superior response rates to single fraction conventional radiotherapy (85-87%) compared to those surviving less than 3 months (44-47%) [94, 95]. Furthermore, patients enrolled in the studies in this review had unusual high performance states, which is a known predictor for good pain response after radiation [96, 97]. As such, the populations reported in the included studies can be assumed to be highly selected. The inclusion of a population with higher than average survival and performance status may result in spuriously high response rates, aligning more closely with those reported for individuals with favorable survival rates.

The impact of treatment fractionation of conventional radiotherapy for pain control in bone metastases has been the focus on extensive international study. Thanks to these studies, the need to ensure comparable outcome reporting was recognized and led to the collaborative development and publication of International Consensus guidelines for the reporting of outcomes [39, 40]. It is, therefore, remarkable that the majority of studies reporting on pain control outcomes after SBRT did not adhere to these guidelines despite most being conducted after 2002. What is more, in most studies it was unclear whether assessable or total treated proportions were re-

ported; both are necessary in this fragile patient population where assessment of pain is complex and survival is limited. Furthermore, adjustment of response rates for concurrent opioid use was often not performed. These two factors had a marked influence on pain response rates, with higher response rates achieved when reporting on assessable lesions and without accounting for narcotic use. In addition, many studies reported only average visual analogue pain scores pre- and post-treatment rather than response rates. Even in studies where SBRT was delivered for pain control, patients with no pain at baseline were included [47, 48, 68, 74].

Where reported, local control was mostly defined as absence of tumor volume change consistent with radiologic progression. While the radiotherapy community is gaining more experience with SBRT, it becomes clear that pseudo-progression and tissue necrosis are important factors to consider after SBRT [53]. As only four studies accounted for pseudo-progression by obtaining confirmatory scans before the lesion was classified as progressing, the local control rate calculated in this meta-analysis might be a conservative estimate. Notably, the factor having greatest influence on local control was fractionation schedule, with superior local control following single fraction SBRT (93% *vs.* 86% after multiple fractions). It is possible that this finding reflects the known impact of hypofractionation upon tumor cell death [98, 99]. Furthermore, fractionated SBRT is particularly important in larger volume lesions, and lesion in close proximity to the spinal cord. For these lesions, full coverage of the target is harder to achieve [100].

Predominantly, 1- and 2-year local control rates were reported. Most studies use Kaplan Meier analysis to determine this rate and thus fail to acknowledge competing risks (*ie,* death before local failure) [101, 102]. Using the Kaplan-Meier approach, those patients who die prior to assessment are censored with an underlying assumption that their local control is equivalent to that of the surviving population – an unobservable assumption not supported by for example Bishop *et al.* Calculating local control by Kaplan-Meier would estimate the local control rate among survivors and is therefore higher than if competing risks were taken into account. We can argue that while the focus is upon the risk of local failure in the surviving population, Kaplan-Meier based analyses may be appropriate. But for a patient, death is a quite relevant event, and the low change of local failure as estimated by accounting for this competing risk, might be worth knowing as information regarding both risk of death and other outcomes is needed. Another statistical issue is that studies investigating local control on a per lesion basis fail to acknowledge the clustered nature of lesions within patients. Multi-level models should be considered to assess outcomes on a lesion level.

Toxicity was generally mild, but most of the toxicity data extracted from the included studies were retrospectively collected and clinician reported, and the implicit limitations must be recognized. In the prospective studies, however, severe toxicity (grade 3 or higher) was reported in only 0.03% of patients. Vertebral compression fracture was not considered in this review

and has previously been reported elsewhere [17]. It is, however, important to realize that SBRT might increase the risk of VCF that would otherwise not occur with crude risk estimates for VCF after spinal SBRT ranging from 11% to 39%. It is hypothesized that SBRT for painful bone metastases may increase the durability of pain responses over conventional radiotherapy. Only four heterogeneous studies reported durability of response [43, 47, 50, 55]. Hunter *et al.* provided comparative outcomes, showing longer duration of pain response after SBRT. The two cohorts reported in this study, however, were not well-matched with the SBRT cohort being younger, with significantly better baseline KPS. Additionally, follow-up was non-standardized and the SBRT cohort had longer median follow-up [50]. Of the four studies, Ryu *et al.* showed the longest duration of pain response (14 months) compared with response after conventional radiotherapy but this study included patients with single isolated spinal metastases, representing a favorable group [47]. As such the potential improvement in response durability with SBRT over conventional radiotherapy has not yet been proven. The two cohort studies which reported quality of life showed an improvement in quality of life after SBRT [34, 48]. The authors did not, however, account for those who were either lost to follow-up or died before assessment. If those with inferior response died quicker or were more likely to be lost to follow-up, which is plausible, then the average qualify of life score will improve over time just reflecting the attrition of patients with poor quality of life. The only (small) randomized study [30] did not find a significant difference in quality of life between conventional and stereotactic radiotherapy after one month. Given the scarcity of data on the impact of SBRT on quality of life, this outcome should be included in future randomized studies.

The strengths of this review include robust estimations of pain response and local control rate and the impact of how these rates are reported based on a systematic study selection. An important limitation of this study is the large heterogeneity of the studies included. Impact of baseline characteristics, including treatment of postoperative patients and re-irradiation, treatment protocols, and study methodology would ideally be examined using meta-regression. However, the lack of consistency in reporting outcomes and failure to completely report the patient characteristics prevented this. Furthermore, it must be recognized that for the majority of patients undergoing palliative radiotherapy for bone metastases pain control and quality of life are the primary outcomes of interest, balanced by aspects of satisfaction with treatment. Local control, whilst easier to assess, is only potentially of importance to a limited cohort with oligometastatic disease.

This systematic review and meta-analysis demonstrates that stereotactic radiotherapy for bone metastases is associated with higher rates of pain response than have previously been reported following conventional radiotherapy. Also, radiological local control rates seem excellent. These improved outcomes, however, may very well be the result of study methodology (*eg,* non-standard response assessments, not accounting for opioid use) and, more important, patient selection by

selecting patients in a good physical condition with longer life expectancy. Large randomized trials are required to formally compare the impact of SBRT and conventional radiotherapy for bone metastases.

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APPENDICES

Appendix 1

Search strategy

"bone and bones" OR bone OR bones OR bony OR skeletal OR osseous OR spine OR spinal

AND

neoplasmata OR metastasis OR metastases OR metastatic OR neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours

AND

radiosurgery OR "stereotactic body radiotherapy" OR "stereotactic body radiation therapy" OR "stereotactic body radiosurgery" OR "stereotactic radiosurgery" OR "stereotactic spinal radiotherapy" OR "stereotactic spinal radiosurgery" OR stereotaxis OR sbrt OR srs OR sbrs OR ssr OR sabr OR "stereotactic ablative"

Appendix 2

Additional figures

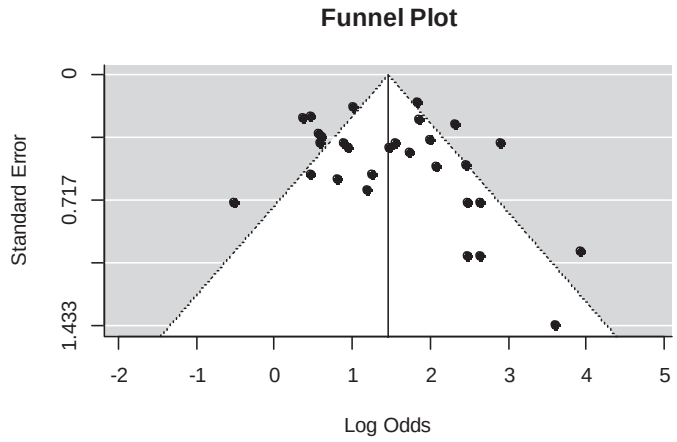

Figure A1. Funnel plot of studies evaluating pain response after SBRT for bone metastases

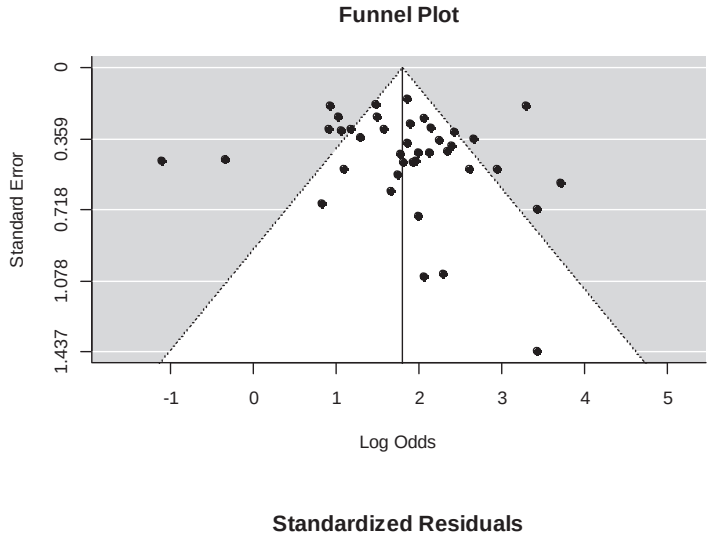

Figure A2. Funnel plot of studies evaluating local control after SBRT for bone metastases

Appendix 3

Summary of Findings: pain response and local control

Table A1. Summary of Findings for studies reporting on pain relief after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A2).

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition	Outcome
Amini et al. 2016‡ [34]	2004-2014	RC	50 lesions	NR	RCC	Mixed	Most common 27 Gy in 3 fractions	Clinical symptoms based on patient report and Wong-Baker Faced pain rating Scale when recorded	Complete response 36.8%; Partial response 44.7%; stable disease 5.3%; and progressive disease 13.2%
Anand et al. 2015 [35]	2010-2012	RC	76 lesions in 52 patients	Patients with and without a prior history of surgery or radiotherapy	Mixed	Spine	14-27 Gy in 1-3 fractions	CR if pain disappeared completely, PR >50% relief on VAS score	Complete response 92.3% and Partial response 5.8% within 3-5 days
Azad et al. 2016 [56]	2005-2013	RC	25 lesions in 25 patients	Patients without a prior history of any treatment to the index site	Mixed	Craniovertebral junction	15-25.5 Gy in 1-5 fractions	NR	Marked decrease or full resolution of pain in 8 patients, no change in 5 patients, 4 patient unknown
Bate et al. 2015 [57]	2007-2011	RC	69 lesions in 57 patients	Patients with or without a prior history of separation surgery	Mixed	Spine	16-30 Gy in 1-5 fractions	NR	Data on pain were available for 45 cases, with an overall VAS score decrease of 3.4 ±2.6 following treatment
Berwouts et al. 2015 [30]	2010-2014	Phase II RCT[1]	15 patients	Patients without a prior history of radiotherapy or treatment with radionuclides	Mixed	Mixed	16 Gy in 1 fraction	According to the International Consensus [40]	Overall response of 60%, overall response 69% in assessable patients only
Chang et al. 2012 [58]	2002-2008	RC	185 lesions in 142 patients	Patients with or without a prior history of radiotherapy to the index site	Mixed	Spine	17.9-23.7 Gy	NR	Pain control rate at 6 months was 86% in the retreatment group, and 93% at the initial treatment group
Choi et al. 2010 [73]	2002-2008	RC	51 lesions in 42 patients	Patients with a history of prior radiotherapy to the index site	Mixed	Spine	10-30 Gy in 1-5 fractions	NR	65% reported significant pain relief, outcome not available in 8 patients, 1 patient without pain relief
Gagnon et al. 2007 [59]	2002-2005	RC[1]	18 patients	Women who failed prior conventional radiotherapy	Breast cancer	Spine	21-24 Gy in 3 fractions	NR	Pain relief within the treated site was judged near-complete in all patients
Garg et al. 2012[1] [36]	2005-2010	PC	63 lesions in 61 patients	Patients with previously unirradiated lesions	Mixed	Spine	18-24 Gy in 1 fraction	NR	More patients experienced reduced pain levels

Table A1. Summary of Findings for studies reporting on pain relief after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A2). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition	Outcome
Germano et al. 2016 [44]	2007-2014	RC	143 lesions in 95 patients	Patients with or without a prior history of surgery and/or radiotherapy	Mixed	Spine	10-18 Gy in 1 fraction	Improvement if at least 2 points decrease on VAS	Pain improvement resulted within 7 days in 100% of the patients with severe pain
Gerszten et al. 2005 [85]	NR	PC	26 lesions in 26 patients	Patients undergoing kyphoplasty-based closed fracture reduction	Mixed	Spine	16-20 Gy in 1 fraction	NR	Long-term improvement in back pain occurred in 24 of 26 patients (92%)
Gerszten et al. 2007 [45]	NR	PC	500 lesions in 393 patients	Patients with or without a prior history of surgery and/or radiotherapy	Mixed	Spine	12.5-25Gy in 1 fraction	Pain score improvement of at least 3 points on VAS score	Overall long-term improvement of in pain in 290 of the 336 cases (86%)
Gibbs et al. 2007 [74]	1996-2005	PC	102 lesion in 74 patients	Patients with or without prior treatment to the index site	Mixed	Spine	16-25 Gy in 1 fraction	NR	In 62 patients with pain and/ or neurological dysfunction, 52 patients (82%) reported improvement or resolution of symptoms
Heron et al. 2012[2] [61]	2000-2008	RC	153 lesion in 104 patients	Patients with or without a history of prior irradiation	Mixed	Spine	20.6-Gy 24.5 in 3-5 fractions	Long-term decrease in pain measured after 4-6 months	73% in multiple fraction group experienced pain relief
Hsu et al. 2015*[62]	2007-2013	RC	32 lesions in 32 patients	Patients with or without prior surgery	Mixed	Spine	7.6-50 Gy in 1-5 fractions	NR	Mean VAS before SBRT was 8.8 and decreased to 2.5 after 1 month
Hunter et al. 2012‡ [50]	2002-2010	RC	76 patients	Patients with or without a history of prior radiotherapy	Mixed	Spine	8-16 Gy in 1 fraction	Scored according to the RTOG 0631 protocol [ref]	Overall pain response 62%, Complete response 33%; Partial response in 29%
Hwang 2012 [46]	2003-2010	PC	11 lesions in 8 patients	Patients with osteoblastic lesions without a prior history of surgery or radiotherapy to the index site	Mixed	Spine	Average 34.5 Gy in 1-6 fractions	At least 2 points decrease after 1 month	All patients had at least 2 points decrease, no patients with pain score of 0
Jhaveri et al. 2012 [55]	2004-2006	RC	24 lesions in 18 patients	Patients with no history of prior surgery or radiotherapy to the index site	RCC	Mixed	18-40 Gy in 3-4 fractions	Patient reported decrease in pain score on VAS at follow-up visits	14 out of 18 patients (78%) had a pain response

Table A1. Summary of Findings for studies reporting on pain relief after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A2). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition	Outcome
Kim et al. 2013 [37]	2009-2010	PC	31 lesions in 22 patients	Patients with or without a history of prior surgery or irradiation	Mixed	Spine	16-30 Gy in 1-5 fractions	According to International Consensus [40]	Complete follow-up at 3 months, CR 52%, PR 19%, SD 26%, PD 3%
Ksiezniak-Baran et al. 2015 [63]	NR	RC	33 lesions in 28 patients	(Oligo)metastatic patients with our without a history of prior surgery	Mixed	Spine	8-40 Gy in 1-3 fractions	NR	11 patient with pain, stable in 5 patients, 3 improved
Lee et al. 2012 [43]	2007-2009	RC	73 lesions in 57 patients	Patients with or without a history of prior surgery or irradiation	Mixed	Spine	15-35 Gy in 1-5 fractions	Decrease of at least 3 points on VAS score without increase in analgesic use, CR if no analgesics or VAS 0-1	Pain relief was achieved in 59 out of 67 painful lesions (88%); Complete response in 34 lesions (51%)
Lee et al. 2013 [64]	2009-2011	RC	51 lesions in 36 patients	Patients with or without a history of prior irradiation	Mixed	Spine	12-36 Gy in 1-6 fractions	NR	Pain relief was assessable in 29 lesions; 72.4% achieved a response within 1 week
Lee E et al. 2015[3] [42]	2008-2012	RC	15 lesions in 13 patients	Patients without a prior history of surgery or radiotherapy with no concurrent systemic treatment	HCC	Spine	18-40 Gy in 1-4 fractions	Pain response if a pain score at follow-up was lower than baseline	Of 13 assessable lesions at 3 months, 12 lesions showed improvement
Lee SH et al. 2015 [42]	2010-2014	RC	63 lesions in 47 patients	Patients without a history of prior surgery	Mixed	Spine	26-42 Gy in 4-6 fractions	Scored according to the RTOG 0631 protocol [ref]	From 46 assessable patients, 10 had CR and 28 patients had PR
Mahadevan et al. 2011 [65]	2005-2008	RC	81 lesions in 60 patients	Patients with radiological and/or clinical progression after prior external beam RT	Mixed	Spine	24-30 Gy in 3-5 fractions	NR	1 month after reirradiation, 22 out of 34 patients with pain had improvement
Massicotte et al. 2012 [75]	2009-2010	PC	10 lesions in 10 patients	Patients treated with minimal access spine surgery followed by SBRT	Mixed	Spine	18-35 Gy in 1-5 fractions	NR	8 patients with back pain; at 1 months post-treatment, median improvement 1 point on VAS, after 5 months median improvement 6 points on VAS

Table A1. Summary of Findings for studies reporting on pain relief after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A2). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition	Outcome
Muacevic et al. 2014 [76]	2005–2009	PC	64 lesions in 40 patients	Highly selected good prognosis subgroup harbouring 1 – 2 metastases, including postoperative or re-irradiation	Prostate	Mixed	16.5-22 Gy in 1 fraction	Pain status was defined by VAS	Pain reduction could be documented in 5 out of 6 painful patients
Napieralski et al. 2016 [67]	2011-2015	RC	71 lesions in 51 patients	Oligometastases or oligo-recurrences	Prostate	Mixed	6-45 Gy in 1-5 fractions	Pain level	At last control, 32 patients with CR, 15 patients with PR, 4 patients with pain
Owen et al. 2014 [77]	2008-2012	PC	85 lesions in 74 patients	Patients with or without a history of prior irradiation	Mixed	Non-spine bone metastases (including sacrum)	15-50 Gy in 1-5 fractions	NR	36 patients with painful lesions, 88% experienced subjective improvement
Park et al. 2015 [68]	2008-2012	RC	59 lesions in 39 patients	Patients with or without a history of prior surgery or irradiation	Mixed	Spine	18-35 Gy in 1-5 fractions	NR	Median pre-SBRT VAS was 4 (range, 0-10), at 1-3 months after SBRT, median VAS of 1 (range, 0-8)
Ryu et al. 2008 [68]	2001-2003	PC	61 lesions in 49 patients	Patients with a single isolated spinal metastasis	Mixed	Spine	10-16 Gy in 1 fraction	CR no pain at 8 weeks without analgesics, PR reduction of pain score of at least 2, PD any increase in pain score or analgesics	Complete response at 8 weeks of 46%; Partial response 18.9%; and stable disease in 16.2%
Schipani et al. 2012 [31]	2005-2008	RC	165 lesions in 124 patients	Patients with 1 or 2 contiguous spine metastases	Mixed	Spine	18 Gy in 1 fraction	NR	114 patients (92%) had improvement in pain and/or neurological symptoms
Sheehan et al. 2009 [90]	NR	RC	110 lesions in 40 patients	Patients with or without a history of prior spinal surgery	Mixed	Spine	10-24 Gy in 1-5 fractions	Pain improvement	Improvement was seen in 34 patients (85%) Note; only 32 patients had pain at baseline
Sohn et al. 2014‡ [38]	2005-2012	RC	At least 31 lesions in 13 patients	Patients without a history of prior treatment	RCC	Spine	Mean dose of 38 Gy in 1-5 fractions	According to International Consensus [ref]	At 1 months, CR in 3 patients (24%) and PR in 7 patients (54%)
Sohn et al. 2016‡ [32]	2005-2012	RC	At least 63 lesions in 28 patients	Patients without a history of prior treatment	HCC	Spine	Mean dose of 36 Gy in 1-5 fractions	According to International Consensus [ref]	At 1 months, CR in 6 patients (21%) and PR in 12 patients (43%)

Table A1. Summary of Findings for studies reporting on pain relief after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A2). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition	Outcome
Staehler et al. 2010* [70]	2005-2009	RC	105 lesions in 55 patients	Patients with progressive disease with a life expectancy of at least 3 months	RCC	Spine	20 Gy in 1 fraction	NR	Median VAS decreased from 5 to 0 within 1 week, only 2 lesions not controlled after 6 months
Tsai et al. 2009 [71]	2005-2007	RC	127 lesions in 69 patients	21% patients received previous radiotherapy	Mixed	Spine	10-30 Gy in 1-5 fractions	NR	Overall VAS improvement was found in 110 lesions
Wang et al. 2012 [48]	2002-2011	PC	166 lesions in 149 patients	Oligometastatic patients, or failure after prior surgery or radiotherapy	Mixed	(Para)spinal lesions	27-30 Gy in typically 3 fractions	Frequency of complete pain relief	After 6 months, 55 of 120 patients (54%) experienced CR

Abbreviations: CR, complete response; Gy, Gray; HCC, hepatocellular carcinoma; NR, not reported; NRS, numeric rating score; RC, retrospective cohort study; PC, prospective cohort study; PD, progressive disease; RCT, randomized controlled trial; RCC, renal cell carcinoma; RT, radiotherapy; PR, partial response; SD, stable disease; VAS, visual analog scale

‡Only results for the SBRT group are included in this Table.

*Only results for patients with bone metastases are included in this Table.

[1]Results on local control are reported in Bishop et al. 2015.

[2]Only the results for the multiple fractions group is included, the results for the single fraction group were reported in Gerszten et al. 2007.

[3]Only the results for patients treated with 1–4 fractions are included in this Table; 12 patients treated with 10 fractions were excluded.

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1).

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Ahmed et al. 2012 [34]	2008-2010	PC	85 lesions in 66 patients	Patients with and without a prior history of radiotherapy and surgery	Mixed	Spine	10-40 Gy in 1-5 fractions	No progressive tumor growth on MRI or PET	89.2% at 1 year
Al-Omair et al. 2013 [72]	2008-2012	PC	80 lesions in 80 patients	Patients who were operated and treated with postoperative SBRT	Mixed	Spine	18-40 Gy in 1-5 fractions	No progression based on MRI	84% at 1 year, time to local failure 19.9 months
Amini et al. 2016‡ [41]	2004-2014	RC	50 lesions	NR	RCC	Mixed	Most common 27 Gy in 3 fractions	No evidence of disease or decrease based on PET, MRI or CT	82.5%, 74.1% and 61.4% at 10, 12 and 24 months
Anand et al. 2015 [35]	2010-2012	RC	76 lesions in 52 patients	Patients with and without a prior history of surgery or radiotherapy	Mixed	Spine	14-27 Gy in 1-3 fractions	Either regression or non-progressive radiological response	Overall response 86.1% with a median follow-up of 8.5 months
Azad et al. 2016 [56]	2005-2013	RC	25 lesions in 25 patients	Patients without a prior history of any treatment to the index site	Mixed	Craniovertebral junction	15-25.5 Gy in 1-5 fractions	Radiographically determined	Lesion size decreased or unchanged in 16 patients, increased in 3 patients, 6 patients unknown
Bahig et al. 2016 [24]	2009-2014	RC	49 lesions in 35 patients	Patients with or without a prior history of surgery	Mixed	Spine	16-35 Gy in 1-5 fractions	Recurrence was defined as continuous tumor volume enlargement on ≥2 serial MRI studies over a period of ≥6 months and/or histologic confirmation	14 spinal segments developed local recurrence at a median time of 15 months, 1-year local control was 87%
Bate et al. 2015 [57]	2007-2011	RC	69 lesions in 57 patients	Patients with or without a prior history of separation surgery	Mixed	Spine	16-30 Gy in 1-5 fractions	Regression or stability of local tumor volume on MRI	94.2% local control at 1 year, 6 patients with local failure
Bishop et al. 2015 [83]	2002-2012[3]	PC	332 lesions in 285 patients	Patients without a prior history of surgery	Mixed	Spine	18-27 Gy in 1-3 fractions	Absence of recurrence, recurrence defined as radiographical progression on MRI	Actuarial 1- and 3-year rates of local control were 88% and 82%, respectively
Chang et al. 2012 [58]	2002-2008	RC	185 lesions in 142 patients	Patients with or without a prior history of radiotherapy	Mixed	Spine	17.9-23.7 Gy	No evidence of mass regrowth on MRI or PET-CT	At 1 year, in the retreatment group 81% and 89% in the initial treatment group

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Chang et al. 2017 [25]	2010-2014	RC	72 lesions in 60 patients	Oligometastatic patients with spinal metastases (up to 3 lesions)	Mixed	Spine	16-52.5 Gy in 1-3 fractions	NR	1-year local progression free survival was 85%
Choi et al. 2010 [73]	2002-2008	RC	51 lesions in 42 patients	Patients with a history or prior radiotherapy	Mixed	Spine	10-30 Gy in 1-5 fractions	Lack of progression within the treated vertebral body on MRI	73% at 1 year
Colaco et al. 2016 [26]	2008-2014	RC	86 lesions with 78 patients	Patients with spinal metastases and concurrent brain metastases	Mixed	Spine	10-27 Gy in 1-3 fractions	Absence of radiological changes suspicious of recurrence of disease on follow-up imaging	1-year local control of 89.4% with a median follow-up of 6 months
Deodato et al. 2013* [84]	NR	PC	8 lesion in 7 patients	NR	Mixed	NR	12-16 Gy in 1 fraction	No progression on CT or MRI according to RECIST criteria, or no increase in metabolic activity on PET	No local failures, 100% overall local control
Germano et al. 2016 [44]	2007-2014	RC	143 lesion in 95 patients	Patients with or without a prior history of surgery and/or radiotherapy	Mixed	Spine	10-18 Gy in 1 fraction	NR	Radiographic control (MRI) was in 94% (116/124) of cases
Gerszten et al. 2007 [45]	NR	PC	500 lesions in 393 patients	Patients with or without a prior history of surgery and/or radiotherapy	Mixed	Spine	12.5-25Gy in 1 fraction	NR	Long-term radiographic control was 90% when used as primary treatment, and 88% when used as 'salvage' technique
Gill et al. 2012 [60]	2005-2010	RC	20 lesions in 20 patients	Patients with oligometastatic disease with or without prior surgery to the index site	Mixed	Spine	30-35 Gy in 5 fractions	No progression of the treated tumor on MRI and/or PET	1- and 2 year local control estimates are 80% and 73% respectively
Hamilton et al. 1996* [86]	NR	PC	8 patients	Patients with or without a history of prior irradiation	Mixed	Spine	8-10 Gy in 1 fraction	NR	No progression in all patients
Heron et al. 2012[1] [61]	2000-2008	RC	153 lesion in 104 patients	Patients with or without a history of prior irradiation	Mixed	Spine	20.6-24.5 Gy in 3-5 fractions	Tumor growth less than 25% was classified as local control	Long-term local control in 89%, at 2 years local control probability of 96%

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Hwang 2012 [46]	2003-2010	RC	11 lesions in 8 patients	Patients with osteoblastic lesions without a prior history of surgery or radiotherapy to the index site	Mixed	Spine	Average 34.5 Gy in 1-6 fractions	Tumor growth less than 10% was regarded local control	10 out of 11 lesions locally controlled
Jahanshahi et al. 2012 [87]	2002-2008	RC	19 lesions	Patients with or without a prior history of surgery	Melanoma	Spine	NR	No local tumor progression	4 lesions CR, 4 stable, 11 unknown
Ksiezniak-Baran et al. 2015 [63]	NR	RC	33 lesions in 28 patients	(Oligo)metastatic patients with our without prior surgery	Mixed	Spine	8-40 Gy in 1-3 fractions	NR	In 17 patients, imaging available, 2 patients with progression
Laufer et al. 2013 [88]	2002-2011	RC	186 lesions in 186 patients	Patients with a history of prior surgery, with or without a history of prior radiotherapy	Mixed	Spine	24-30 Gy in 1-6 fractions	NR	Local control at 1 year 83.6%, local progression in 34 patients
Lee et al. 2013 [64]	2009-2011	RC	51 lesions in 36 patients	Patients with or without a history of prior irradiation	Mixed	Spine	12-36 Gy in 1-6 fractions	Absence of disease progression on follow-up images	Local control at 1 year 88.2%, 6 cases of local failure
Lee E et al. 2015 [42]	2008-2012	RC	15 lesions in 13 patients	Patients without a prior history of surgery or radiotherapy with no concurrent systemic treatment	HCC	Spine	18-40 Gy in 1-4 fractions	Evaluated according to RECIST v1.1 and PERCIST v1.0, CR and PR were regarded radiological response	At 3 months, all lesions showed CR (n=7), PR (n=5) or SD (n=3), 1 year local control rate 78.6%
Lee SH et al. 2015 [51]	2010-2014	RC	63 lesions in 47 patients	Patients without a history of prior surgery	Mixed	Spine	26-42 Gy in 4-6 fractions	Absence of local tumor growth on MRI	Out of 27 assessable patients, local failure occurred in 4 lesions
Mahadevan et al. 2011 [65]	2005-2008	RC	81 lesions in 60 patients	Patients with radiological and/or clinical progression after prior external beam radiotherapy	Mixed	Spine	24-30 Gy in 3-5 fractions	NR	At last follow-up, 56 out of 60 patients had improved or stable disease in their scans

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Massicotte et al. 2012 [75]	2009-2010	PC	10 lesions in 10 patients	Patients treated with minimal access spine surgery followed by SBRT	Mixed	Spine	18-35 Gy in 1-5 fractions	NR	3 patients had disease progression
McDonald et al. 2015 [66]	2011-2014	RC	42 lesions in 33 patients	Oligometastatic or oligo-progressive patients	Mixed	Non-spine bone	20-50 Gy in 1-5 fractions	Lesions that were classified as SD, PR, or CR according to RESIST v1.1 or MDA criteria	Overall local control according to RECIST of 36 out of 42 lesions ((86%), and 35 out of 42 lesions (83%) according to MDA criteria
Miller et al. 2016 [27]	2006-2015	RC	151 lesions in 100 patients	Patients with spinal metastases with or without concurrent treatment with TKIs	RCC	Spine	10-24 Gy in 1-3 fractions	Any in-field progression as evaluated by neuro-radiologists were considered local failure	At 12 months, local failure was lowest among patients treated with first-line TKI
Muacevic et al. 2014 [76]	2005–2009	PC	64 lesions in 40 patients	Highly selected good prognosis subgroup harbouring 1 – 2 metastases, including postoperative or re-irradiation	Prostate	Mixed	16.5-22 Gy in 1 fraction	Local failure if tumor growth on MRI or increased tracer uptake in choline PET-CT	Actuarial 6-, 12- and 24 months local tumor control rate was 95.5%
Napieralski et al. 2016 [76]	2011-2015	RC	71 lesions in 51 patients	Oligo-metastases or oligo-recurrences	Prostate	Mixed	6-45 Gy in 1-5 fractions (only 1 patient 6 Gy, 1 patient 8 Gy)	Lack of in-field progression	Follow-up available in 47 patients with 15 lesions in 10 patients progressed, 1 year local control rate 70%
Nikolajek et al. 2011* [67]	2005-2009	PC	41 patients	Patients with prior irradiation	Mixed	Spine	10-28 Gy in 1 fraction	Using RESIST criteria, local control defined as CR or PR	6 patients with a local failure
Owen et al. 2014 [77]	2008-2012	PC	85 lesions in 74 patients	Patients with or without a history of prior irradiation	Mixed	Non-spine bone metas-tases	15-50 Gy in 1-5 fractions	Stable disease, PR or CR based on serial imaging with CT, MRI, or PET	7 patients with in-field recurrence, 1 year local control rate of 91.8%

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Park et al. 2015 [68]	2008-2012	RC	59 lesions in 39 patients	Patients with or without a history of prior surgery or irradiation	Mixed	Spine	18-35 Gy in 1-5 fractions	No tumor progression on imaging, or no salvage treatment	4 patients experienced local recurrence, 1 year local control rate 93.2%
Sahgal et al. 2009 [69]	2003-2006	RC	60 lesions in 37 patients	Patients with or without a prior history of surgery or irradiation	Mixed	Spine	7-40 Gy in 1-5 fractions	No progression based on imaging and/or symptoms	8 of 60 tumors recurred, 1 year PFS 85%
Schipani et al. 2012 [31]	2005-2008	RC	165 lesions in 124 patients	Patients with 1 or 2 contiguous spine metastases	Mixed	Spine	18 Gy in 1 fraction	NR	Local control in 114 patients (92%)
Sheehan et al. 2009 [90]	NR	RC	110 lesions in 40 patients	Patients with or without prior spinal surgery	Mixed	Spine	10-24 Gy in 1-5 fractions	Volume increase on MRI	Increase in volume in 20 lesions (18%)
Sohn et al. 2014‡ [38]	2005-2012	RC	At least 31 lesions in 13 patients	Patients without a history of prior treatment	RCC	Spine	Mean dose of 38 Gy in 1-5 fractions	NR	Local control rate at 1 month of 100%, at 1 year of 85.7%
Sohn et al. 2016‡ [32]	2005-2012	RC	At least 63 lesions in 28 patients	Patients without a history of prior treatment	HCC	Spine	Mean dose of 36 Gy in 1-5 fractions	NR	Local control rate at 1 month of 92%, at 1 year of 25%
Staehler et al. 2010* [70]	2005-2009	RC	105 lesions in 55 patients	Patients with progressive disease with a life expectancy of at least 3 months	RCC	Spine	20 Gy in 1 fraction	NR	Local control rate after 12 months 94.1%
Thibault et al. 2014 [53]	2007-2012	PC	71 spinal segments in 37 patients	Patients with or without a history of surgery or irradiation	RCC	Spine	18-30 Gy in 1-5 fractions	Local progression based on radiologist's interpretation of MR images	Local progression in 12 of 71 spinal segments
Thibault et al. 2015 [54]	2009-2013	PC	56 lesions in 40 patients	Patients initially treated with SBRT who subsequently experienced local tumor progression	Mixed	Spine	20-35 Gy in 2-5 fractions	Local failure was defined as any tumor volume change consistent with radiologic progression	13 of 56 segments (23%) progressed locally, 12-months local control rate 80.6%

Table A2. Summary of Findings for studies reporting on local control after SBRT. The studies with a gray background report outcomes for pain response as well as for local control (see Table A1). (*continued*)

Author, Year	Enrolment period	Study type	Sample size (lesion/ patients)	Study population	Primary tumor	Location	Dose, Fractions	Outcome definition of local control	Outcome
Tsai et al. 2009 [71]	2005-2007	RC	127 lesions in 69 patients	21% patients received prior radiotherapy	Mixed	Spine	10-30 Gy in 1-5 fractions	NR	Local failures were observed in 3 patients, 10-months local control was 96.8%
Ursino et al. 2016 [33]	2010-2013	RC	40 lesions in 40 patients	Oligometastatic patients without a history of surgery or irradiation	Mixed	Mixed	24 Gy in 1 fraction or 27 Gy in 3 fractions	NR	5 of 40 patients with a recurrence (12.5%)
Yamada et al. 2017 [28]	2003-2015	RC	881 lesions in 657 patients	Patients without a history of prior surgery or radiotherapy	Mixed	Spine	16-26 Gy in 1 fraction	No enlargement of the treated tumor on imaging studies or positive pathological findings after treatment	28 lesions progressed, with a 24-months local failure rate of 3.1%

Abbreviations: CR, complete response; CT, computed tomography scan; Gy, Gray; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; MSCC = malignant spinal cord compression; NR, not reported; PC = prospective cohort study; PD, progressive disease; PET, positron emission tomography; PFS, progression free survival; PR, partial response; RC = retrospective cohort study; RCC, renal cell carcinoma; SBRT, stereotactic body radiotherapy; SD, stable disease; TKI = tyrosine kinase inhibitors

‡Only results for the SBRT group are included in this Table.

*Only results for patients with bone metastases are included in this Table.

[1]Only the results for the multiple fractions group is included, the results for the single fraction group were reported in Gerszten et al. 2007.

CHAPTER 8

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

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ABSTRACT

Background

Standard radiotherapy is the treatment of first choice in patients with symptomatic spinal metastases, but is only moderately effective. Stereotactic body radiation therapy is increasingly used to treat spinal metastases, without randomized evidence of superiority over standard radiotherapy. The VERTICAL study aims to quantify the effect of stereotactic radiation therapy in patients with bone metastases.

Methods/design

This study follows the 'cohort multiple Randomized Controlled Trial' design. The VERTICAL study is conducted within the PRESENT cohort. In PRESENT, all patients with bone metastases referred for radiation therapy are enrolled. For each patient, clinical and patient-reported outcomes are captured at baseline and at regular intervals during follow-up. In addition, patients give informed consent to be offered experimental interventions. Within PRESENT, 110 patients are identified as a sub cohort of eligible patients (*ie*, patients with unirradiated painful, mechanically stable spinal metastases who are able to undergo stereotactic radiation therapy). After a protocol amendment, also patients with non-spinal bony metastases are eligible. From the sub cohort, a random selection of patients is offered stereotactic radiation therapy (n = 55), which patients may accept or refuse. Only patients accepting stereotactic radiation therapy sign informed consent for the VERTICAL trial. Non-selected patients (n = 55) receive standard radiotherapy, and are not aware of them serving as controls. Primary endpoint is pain response after three months. Data will be analyzed by intention to treat, complemented by instrumental variable analysis in case of substantial refusal of the stereotactic radiation therapy in the intervention arm.

Discussion

This study is designed to quantify the treatment response after (stereotactic) radiation therapy in patients with symptomatic bone metastases. This is the first randomized study in palliative care following the cohort multiple Randomized Controlled Trial design. This design addresses common difficulties associated with classic pragmatic randomized controlled trials, such as disappointment bias in patients allocated to the control arm, slow recruitment, and poor generalizability.

Trial registration

The Netherlands Trials Register number NL49316.041.14. ClinicalTrials.gov registration number NCT02364115. Date of trial registration February 1, 2015.

BACKGROUND

Bone metastases are a frequent distant manifestation of cancer, with the spinal column being the most common site [1]. Spinal metastases can induce cancer-related pain, mechanical instability, and neural compression, thereby causing morbidity and impacting on quality of life (QOL). Treatment is aimed at pain relief and prevention of neurological deficits. The treatment for most patients with symptomatic spinal metastases is standard external beam radiotherapy [2], which is moderately effective: around 60% of patients who undergo external beam radiotherapy experience pain relief [3]. Furthermore, pain relief is often incomplete with complete pain response rates ranging from 0 and 23% [3] and one in five patients needs reirradiation [4]. Escalating the dose to the metastatic site might improve the pain response and prolong the duration of pain relief [5]. Dose escalation to spinal tumors using standard radiotherapy is complicated by the low tolerance of the spinal cord to radiation. Stereotactic body radiotherapy (SBRT) is able to deliver precise high-dose radiation to spinal metastases in single or multiple fractions, while sparing surrounding healthy tissues. Phase I and II studies have suggested that, for selected groups of patients, SBRT for spinal metastases may be accurate, safe, and effective [5, 6], with complete pain response in 54% of patients six months after SBRT [7]. Other authors even reported overall pain response rates around 90% [8–10]. To date however, no randomized controlled studies have been performed so equipoise still exist on the effectiveness of SBRT in comparison to standard radiotherapy. Therefore, we designed a pragmatic randomized controlled trial to compare conVEntional RadioTherapy with stereotactIC body radiotherapy in patients with spinAL metastases (VERTICAL) following the CONSORT statement [11].

METHODS/DESIGN

Study design

This study is conducted within the Prospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort [12]. All patients with bone metastases referred to the departments or radiation oncology or orthopedic surgery of the University Medical Center Utrecht are asked to participate in this prospective, observational cohort. Baseline and follow-up data are collected from clinical files, and patient-reported outcomes (PROMs, *i.e.* a pain inventory and QOL questionnaires) are collected at fixed time intervals. This study follows the cohort multiple randomized controlled trial (cmRCT) design as described by Relton *et al.* [13].

Patient recruitment

At enrollment, patients give informed consent for collection of clinical and survival data, and can opt-in to provide PROMs. In addition, in a separate question, we ask patients for their broad consent for future randomization in trials that will investigate the effectiveness of experimental treatments [14]. Patients within the PRESENT cohort who meet the VERTICAL inclusion

criteria (Table 1) are identified as a sub cohort of eligible patients. Eligible patients are PROMs-providing participants of the PRESENT cohort, have untreated symptomatic spinal metastases, and have given consent for broad randomization to experimental interventions. Patients are excluded if they are not able to undergo SBRT, have severe or progressive neurological deficits, received previous radiotherapy or surgery to the index site(s), or have a life expectancy less than three months. After a protocol amendment on September 23, 2015 to adjust to developments in clinical practice, also patients with non-spinal bony metastases are eligible.

Random selection

Eligible patients are randomly selected from the sub cohort on a 1:1 basis with varying block sizes (n = 6 or 8) using an in-house randomization computer program. The radiation oncologist will offer the experimental intervention (*ie,* SBRT) to the randomly selected patients. If they accept the treatment offer, they will sign informed consent for participation in the VERTICAL study. Patients who refuse the SBRT will receive care as usual (*ie,* standard radiotherapy). According to the cmRCT design, patients in the sub cohort who are not randomly selected will not be informed about the experimental intervention, nor will they be informed about their participation in the control arm of the VERTICAL study. Outcomes in randomly selected patients are compared with the outcomes in eligible patients not randomly selected who received standard radiotherapy (Figure 1).

Table 1. Selection criteria for the VERTICAL study

Inclusion criteria	Exclusion criteria
Participant in PRESENT cohort	Lesion in C1, and C2
Filling out PRESENT-questionnaires	Contraindication for MRI
Broad consent for randomization to experimental interventions	Radiosensitive histology such as multiple myeloma
Histologic proof of malignancy	Unable to undergo SBRT treatment
Imaging evidence of spinal metastases	Patient with < 3 months life expectancy
Per lesion no more than 3 consecutive spine segments involved with one unaffected vertebral body above and below	Chemotherapy or systemic radionuclide delivery within 24 hours before and after SBRT
No more than 2 painful lesions needing treatment	Previous EBRT or SBRT to same level
No compression of spinal cord	Unstable spine requiring surgical stabilization
No or mild neurological signs[a]	Severe, worsening or progressive neurological deficit
KPS > 50 and pain score > 3[b]	

VERTICAL, randomized controlled trial comparing conVEntional RadioTherapy with stereotactIC body radiotherapy in patients with spinAL metastases; PRESENT, Prospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort; MRI, magnetic resonance imaging; SBRT, stereotactic body radiotherapy; EBRT, external beam radiotherapy; KPS, Karnofsky performance score
[a] radiculopathy, dermatomal sensory change, and muscle strength of involved extremity is Medical Research Counsil (MRC) 4/5
[b] on a scale from 0 to 10

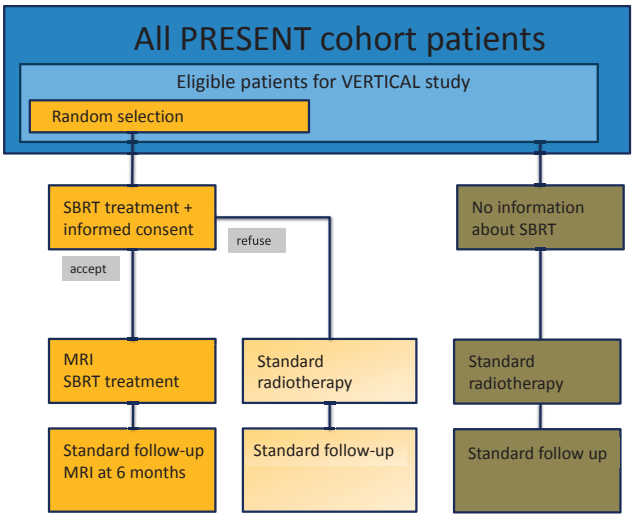

Figure 1. Study design VERTICAL study A large observational cohort of patients with bone metastases is recruited and their outcomes regularly measured (dark blue box). Patients within the PRESENT cohort who meet the VERTICAL inclusion criteria are identified as a sub cohort of eligible patients (light blue box). Randomly selected patients (orange box) are offered the SBRT intervention. The outcomes of these randomly selected patients (*ie*, the intervention arm) are then compared with the outcomes of eligible patients not randomly selected who receive standard of care (*ie*, the control arm, brown boxes).

Standard radiotherapy

Standard radiotherapy for symptomatic bony metastases consists of single fraction external beam radiotherapy of 8 Gray (Gy). The radiation oncologist might however choose a multi-fraction regime of 30 Gy in 10 fractions if the patient has a favorable primary tumor (*ie*, breast or prostate cancer), a Karnofsky performance score (KPS) of 80–100%, and absence of visceral or brain metastases. The radiation dose distribution usually consists of a single field in posteroanterior direction with the normalization point (100% isodoseline) at 6 cm for a 6 MV photon beam and at 6 or 7 cm for a 10 MV photon beam. The vertebral body should at least receive 80% of the prescribed dose. If necessary, a field in anteroposterior direction is added to the posteroanterior field. Metastases in the cervical spine are usually treated with two lateral opposing fields. The leafs of the multileaf collimator are used to adjust the shape of the treatment field. Prior to treatment, cone beam computed tomography (CBCT) scan images are obtained to verify that the position of the patient is correct with regard to the planning computed tomography (CT). Currently, our department is working on the clinical implementation of auto-planning for single fraction treatment of patients with bone metastases. Automatic treatment plans will then be delivered to the spinal metastases using intensity-modulated radiation therapy (IMRT) technique.

Stereotactic body radiotherapy

Patients in the experimental arm undergoing SBRT are immobilized with an S-frame thermoplastic mask in case of skull or cervical spine tumors extending to the upper thoracic (T3) vertebral body. In case of lower thoracic and lumbar lesions, and rib and pelvic lesions, they are immobilized using a vacuum mattress (BlueBAG™, Elekta, Stockholm, Sweden). Magnetic resonance imaging (MRI) is used to delineate the gross tumor volume (GTV), clinical target volume (CTV), and the organs at risk (OAR). We use MRI guidance to deliver stereotactic radiotherapy to the visible metastasis (*ie,* GTV) exclusively. With the aid of T1 weighted, T2 weighted, and diffusion weighted imaging (DWI) sequences, it is possible to delineate the GTV accurately [15, 16]. Adjacent normal appearing bone may harbor subclinical disease and could potentially serve as a source for a local recurrence [17]. Therefore, the bony compartment containing the GTV (*ie,* the CTV, which consists of the entire vertebral body, pedicle, transverse process, lamina, or spinous process) is prescribed 8 Gy in order to treat subclinical disease whereas the metastasis receives 18 Gy (Figure 2). This simultaneous integrated boost approach has the potential advantage of lowering the risk of vertebral compression fractures by sparing the unaffected, healthy bone tissue surrounding the metastasis while also treating subclinical disease. When necessary, an equivalent dose may be given using another fractionation schedule: 30 Gy in three fractions to the visible metastasis with 15 Gy in three fractions to the bony compartment or 35 Gy in five fractions with 20 Gy in five fractions to the bony compartment. Possible reasons to fractionate the dose might be proximity of visible metastasis to the spinal cord or more than two consecutive spine segments involved. Treatment planning is performed on pretreatment CT and MRI scans that are co-registered to yield information on all relevant structures for assessing dose distribution. Volumetric modulated arc therapy (VMAT) treatment plans are generated for SBRT patients. Dose constraints are set for the OAR based on institution specific guidelines. These constraints, and particularly the constraint of the spinal cord, are of primary concern. If necessary, dose deliverance to the GTV will be limited in order to meet these constraints [18]. For all patients, an online CBCT scan is acquired with the patient in treatment position on the treatment couch just before start of the irradiation. The CBCT scan yields the exact position of

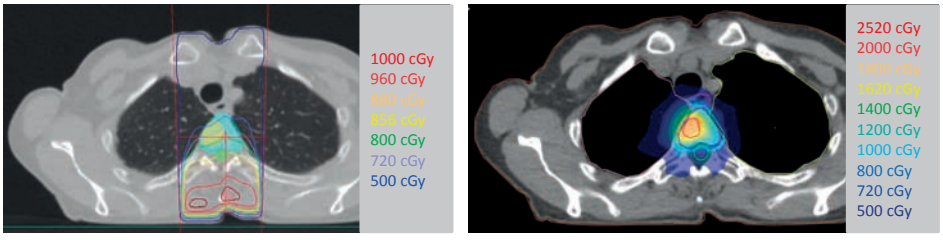

Figure 2. Standard radiotherapy and stereotactic body radiotherapy Comparison of a conventional radiation dose distribution using standard radiotherapy (left) with a spinal stereotactic radiotherapy simultaneous integrated boost distribution (right) in a patient with a T4 vertebral body metastasis from breast cancer

the bony anatomy and is registered to the pretreatment CT and MRI data. The alignment of the patient, or more specifically the affected vertebra bodies, on the CBCT scan is compared with the pre-treatment CT and MRI scans. After possible correction a second CBCT is performed between the two VMAT arcs. A third CBCT is taken post-treatment to document stability of the target during treatment.

Primary endpoint

Primary endpoint of this study is complete or partial pain response at three months. Pain response is defined according to the International Bone Metastases Consensus Endpoints for Clinical Trials (Table 2) [19]. A pain score of zero with no concomitant increase in analgesic intake compared to baseline is defined as complete response. Partial response is pain reduction of at least 2 points on a scale of 0–10 without increase in analgesic intake and/or analgesic reduction of at least 25% from baseline without an increase in pain. Pain progression is defined as an increase in pain score of at least two points above baseline with stable analgesic use and/or as baseline with at least stable pain scores. All responses not captured with complete and partial response or pain progression are considered indeterminate response. Pain is measured by the Brief Pain Inventory (BPI), which has been validated for use in advanced cancer patients to assess pain and functional interference stemming from bone metastases [20].

Table 2. Response rate to radiotherapy according to the international consensus [19]

Responders	
Complete response	Pain score of 0 and stable or reduced OMED
Partial response	Pain reduction of 2 points on a 0–10 scale or more and/or OMED reduction by 25% or more
Non-responders	
Pain progression	Increase of 2 points on a 0–10 scale or more above baseline, and/or OMED increased by 25% or more
Indeterminate response	Any response including stable disease that is not captured by complete or partial response or pain progression

OMED, daily oral morphine equivalent

Secondary endpoints

Secondary endpoints include local tumor control, duration of pain response, toxicity, vertebral compression fractures, QOL, and overall survival. Evaluation of local tumor control will be based on imaging acquired during follow-up. Duration of pain response starts at response until pain progression or end of follow-up using information provided by the BPI. A radiation oncologist records toxicity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 [21] 6 weeks after radiation treatment. Toxicity occurring after 6 weeks, (serious) adverse events (SAEs), and hospitalization are registered in the context of the PRESENT cohort. Information about toxicity is based on clinical follow-up data and biannual patient-administered questionnaires on health status and hospitalization. All patients in

the SBRT arm undergo an additional MRI scan six months after radiation in order to assess vertebral compression fractures. Since most compression fractures occur 4 months after radiation treatment [22], this 6-month-MRI captures most incidents. In case of clinical suspicion of a vertebral compression fracture, obtaining the MRI scan will be advanced as deemed appropriate. Quality of life is measured by the EORTC QLQ-C15-PAL general questionnaire [23] and the bone metastases-specific module, the EORTC QLQ-BM22 [24]. The EORTC QLQ-C15-PAL is an abbreviated 15-item version of the EORTC QLQ-C30 specially developed for use in palliative care. In order to evaluate the cost-effectiveness, patients are also provided with the EQ-5D questionnaire. Patients fill out these QOL questionnaires and the BPI before the start of radiation treatment (baseline) and after one, two, three, and six months, and every six months thereafter. The BPI is provided after two and six weeks as well. We make use of the digital patient tracking system PROFILES, so patients are able to complete the questionnaires online after secured login [25]. Overall survival is monitored within the PRESENT cohort by clinical follow-up and via an electronic link with the Municipal Personal Records Database.

Safety

We will report treatment induced SAEs within 15 days following notification through a government based internet portal to the accredited institutional review board that approved the protocol. Treatment induced SAEs that result in death or are life threatening will be reported within seven days.

Sample size considerations

Based on the most recent meta-analysis, we expect a pain response in 60% of patients following standard radiotherapy [3]. Pain response after stereotactic radiotherapy is assumed to be 85% [8, 9]. We expect that approximately 90% of patients who are offered SBRT treatment, will accept the offer. Cross-over from control arm to the SBRT treatment arm is extremely unlikely, since only patients who are randomly selected to receive SBRT are informed about the treatment. Taking a one-sided α of 5% and a power of 80%, we require 49 patients per treatment arm to show a statistically significant difference of 15% in pain response. The reason to choose a one sided α is that, although improbable, inferior pain response after stereotactic treatment would lead to the same action as no difference at all between the two treatment regimen. This is because the SBRT treatment will only be implemented if it is significantly better than the usual care, since SBRT treatment is more complex, less convenient for patients, and more expensive than standard radiotherapy. Finally, to allow for a 10% drop out rate, recruitment of 55 patients per group is intended. We expect to complete recruitment within 18 months based on the number of patients we treat in our center annually.

Data analysis

Data will be analyzed according to the intention to treat principle. Data of eligible patients who were randomly offered stereotactic radiotherapy will be compared with eligible patients who were not randomly selected and received standard radiotherapy. In case of dropout (*ie,* patients not surviving longer than three months or patients unable to provide pain scores and analgesic use), a worst-case analysis will be performed: dropped-out patients will be classified as non-responders. In case of substantial refusal of the SBRT offer in the intervention arm, instrumental variable analysis will be used to account for non-compliance [26]. The primary outcome (*ie,* proportion of patients with response to radiotherapy) will be presented in absolute numbers and proportions. Differences in pain response will be compared by $\chi 2$ test. If randomization fails, imbalances between baseline characteristics will be adjusted by logistic regression analysis. Differences in duration of response and overall survival will be analysed by Kaplan-Meier analysis and log rank test. Toxicity will be presented as the overall incidence of grade 3–4 toxicity and incidence of vertebral compression fractures. Differences will be tested with the $\chi 2$ test. A comparison in QOL will be made between the baseline QOL and at predefined intervals after treatment. A change of 10% of the scale breadth will be considered a clinically relevant change of QOL [27]. Data will be presented as improved (≥10% increase), stable, or worsened (≥10% decrease) QOL. We will evaluate the pattern of QOL as a continuous outcome over time using mixed models. Differences with a p-value <0.05 will be considered statistically significant. We have planned to perform an interim analysis after inclusion of half of the patients (*ie,* 55 patients) when they have completed their follow-up (*ie,* three months pain assessment).

DISCUSSION

In this report, we present the rationale and design of the VERTICAL trial. In this randomized study, we investigate whether SBRT can increase the proportion of patients with (complete or partial) pain response. Although standard radiotherapy is moderately effective in achieving pain relief in most patients with spinal metastases, up to 40% of patients do not experience any pain relief and complete response occurs in only 30% of responders [3]. Presently, it is not exactly understood why some patients do not respond (adequately) to standard radiotherapy. A factor that may play a role in the suboptimal response to standard radiotherapy is the way the radiation dose is delivered. Barton *et al.* [28] showed that the dose received by the vertebral column using standard radiation techniques varies by up to 50%. For instance, when using a direct postero-anterior field to deliver 8 Gy at a depth of 5 cm, metastases located in deep vertebrae receive less than 50% of the prescribed dose. This is important, since 4 Gy in one fractions is proven to be less effective than 8 Gy [29–31]. If there is indeed a threshold dose below which pain relief is less likely and of slower onset, it may be important to ensure that the vertebral metastasis receives the dose intended. However, the low tolerance of the spinal cord to radiation limits the standard radiation dose to a level that below the optimal therapeutic dose thus providing a less

than optimal response. Precise confinement of the radiation dose, even including dose escalation in addition, should increase the probability of pain relief while the risk of injury to the spinal cord is minimized. Several retrospective and prospective phase II studies have indeed shown the safety and efficacy of SBRT in spinal metastases [5, 6].

Most studies on spinal SBRT included a heterogeneous patient population, including previously unirradiated patients, patients who needed reirradiation, and postoperative SBRT, and these categories include patients with or without solitary spine metastases [8, 32]. We include all unirradiated patients with spinal metastases including patients with diffuse metastases, and mild neurological complaints. In this way, we deliberately chose a pragmatic approach since we expect that this would be the patient population that is going to be treated once the benefits of SBRT would have been established. In order to investigate the effect of SBRT without the effect of additional treatments, we however exclude patients who received previous standard or stereotactic body radiotherapy or surgery to the index site. As pragmatic trials investigate the effectiveness of medical treatment strategies under usual conditions, the standard strategy (*ie,* 8 Gy in a single fraction, or for selected patients 30 Gy in 10 fractions) will be compared to the SBRT strategy (which includes more dose schedules). Still, the biological effective dose (BED) of the three dose regimen is much higher compared to the BED of the conventional dose regimen. If there is a difference in pain response after SBRT compared to standard radiotherapy, we should be able to detect that differences despite the use of multiple radiation dose schedules. Traditionally, stereotactic radiotherapy in metastatic bone disease is intended for patients with spinal metastases. However, SBRT is increasing being applied in the treatment of non-spine osseous metastases [33]. Since spinal metastases are similar to non-spine osseous metastases in terms of bone involvement and pain relief after standard radiotherapy [34, 35], the response after SBRT in spinal and non-spine osseous metastases is likely to be similar as well. Therefore, we have extended the VERTICAL inclusion criteria to patients with non-spinal bony metastatic disease.

To our knowledge, six other randomized studies on spinal SBRT are currently being conducted (Table 3) [36–41]. Only two other trials require both CT and MRI imaging for the delineation of the spinal metastases [37, 38], however, these trials delineate the whole bony compartment (*ie,* the CTV) that contains the metastasis instead of using an simultaneous integrated boost approach. They also have strict instructions on how to apply the standard and stereotactic body radiotherapy in contrast to our more pragmatic approach, offering radiation oncologists leeway in fractionation schedule. Furthermore, the VERTICAL trial distinguishes itself from these trials by applying the cmRCT design. The cmRCT design was proposed as a variant of classic pragmatic randomized difficulties associated with those RCTs, such as disappointment bias, drop-outs, slow recruitment, and poor generalizability [13]. Patients and doctors often have a strong preference for the experimental treatment that has not proven to, but is expected to

be superior. Investigators of the RTOG 0631 trial indeed experience that patients and their physicians prefer the SBRT treatment over standard radiotherapy [Samuel Ryu, personal communication]. Consequently, patients allocated to the standard arm may show disappointment when reporting outcomes. This is of particular concern since the primary endpoint consists of a subjective outcome (*ie,* pain scores). By using the cmRCT design however, control patients are unaware of being allocated to the control arm, which will prevent disappointment bias in observed outcomes. Furthermore, standard of care is likely to be unaffected by treatment allocation and will therefore better resemble routine practice. We also expect lower drop-outs rates since patients in the control arm are not likely to withdraw from standard care, which may be

Table 3. Randomized trials on SBRT for spinal metastases[a]

Name, *institution*	Start date, *sample size*	Patients	SBRT treatment	Comparator	Primary Endpoint
Mahadevan et al. [36] *Beth Israel Deaconess MC*	01–2012 *81*	Number of sites not stated; Pain ≥ 5; No rapid neurologic decline	Total dose unknown in 1, 3, or 5 fractions; No more information provided	Standard EBRT in 10 fractions	Pain response[b]
RACOST [37] *Radboud UMC Nijmegen*	06–2015 *382*	Number of sites not stated; May have other visceral metastases; Pain ≥ 5; No neurologic deficit	Any modern system; 20 Gy in one fraction; Delineation with MRI and CT; Target volume is GTV, with bony CTV expansion, PTV margin ≤ 3 mm	Standard EBRT single dose of 8 Gy, no restrictions to radiation technique	Pain response taking administration of opioids into account[b]
RTOG 0631 [38] *Henry Ford Hospital*	11–2011 *395*	Up to 3 spinal sites; May have other visceral metastases; Pain ≥ 5; No rapid neurologic decline	IMRT or other dose painting technique; 16 or 18 Gy in one fraction; Delineation with MRI and CT; Target volume is involved VB	Standaard EBRT single dose of 8 Gy, 2D and 3D conformal therapy	Pain response (increase or decrease of ≥ 3 points) at 3 months
SMART [39] *Heidelberg University*	12–2014 *60*	Up to 2 spinal sites; No neurologic deficit	IMRT; 24 Gy in one fraction; Delineation with CT; Target volume is involved VB with PTV margin	Standard EBRT 30 Gy in 10 fractions, 3D conformal planning	Pain response (increase or decrease of > 2 points) at 3 months
SPIN-MET [40] *University of Erlangen-Nürnberg*	03–2013 *155*	Number of sites not stated; May have other visceral metastases; No rapid neurologic decline	36 Gy in 12 fractions plus integrated boost 48 Gy in 12 fractions; No more information provided	Conventional EBRT 30 Gy in 10 fractions	Tumor control defined as time to progression on MRI
Tingting et al. [41] *Cancer Hospital of Shantou UMC*	03–2014 *100*	Up to 3 spinal sites	24 Gy in 2 fractions; No more information provided	Conventional EBRT 30 Gy in 10 fractions	Pain response taking administration of opioid into account[b]
VERTICAL *University Medical Center Utrecht*	01–2015 *110*	Up to 2 spinal sites; May have other visceral metastases; Pain ≥ 3; no rapid neurologic decline	VMAT; 18 Gy in one fraction or fractionated equivalent; Delineation with MRI and CT; Target volume with differential dosing	Standard of care for standard radiotherapy	Pain response (increase or decrease of ≥ 2 points) taking administration of opioid into account at 3 months

CT, computed tomography; CTV, clinical target volume; EBRT, external beam radiotherapy; IMRT, image guided radiotherapy; GTV, gross tumor volume; MC, medical center; MRI, magnetic resonance imaging; PTV, planning target volume; VB, vertebral body

[a]Excluding studies on oligometastases including spinal oligometastatic disease, comparing surgery with SBRT, and studies including non-spinal lesions as well

[b]Time point at which endpoint is measured not given

of particular interest in this fragile patient population. Because of this fragility, researchers in this field should make an effort to optimize recruitment rates. The use of the cmRCT design may foster recruitment rates by its unique informed consent procedure. A reason not to take part in classic randomized studies might be that patients cannot be guaranteed to receive the desired experimental treatment. Furthermore, once participating, patients are often allowed to participate in one trial at a time only. By contrast, patients participating in a cmRCT study give broad informed consent to participate in randomized trials, but not to specific trials which may increase recruitment rates. Moreover, the cmRCT cohort offers an infrastructure which allows the conduct of randomized trials simultaneously. Finally, recruitment in cohort studies is usually more manageable compared with recruitment in RCTs. The inclusion rates in the PRESENT cohort for example are promising: the participation rate is 83%, and 88% of the participating patients have given informed consent for broad randomization to experimental interventions. The use of a cohort in cmRCT studies offers more potential advantages. Palliative patients willing to participate in randomized trials often represent a relatively healthier and higher-educated subgroup. By using a cohort as a recruitment pool for RCTs, a more routine population is included since recruitment for cohort studies is generally less selective. Moreover, the cohort provides information on baseline characteristics and outcome measurements (*ie,* the regular cohort measures) of drop-outs, which is essential in the data analysis. Patients allocated to the control arm, are cohort participants who receive the current standard of care (*ie,* standard radiotherapy in the PRESENT case). In our department, the standard of care for patients with bone metastases will change from standard radiotherapy to automatically generated conformal treatment plans. Would the VERTICAL trial have been conventionally conducted, this could have been problematic since control patients in the VERTICAL trial would then have been withhold from standard of care. However, the cmRCT design has the advantage that experimental interventions are compared with the most up-to-date standard of care, instead of competing with outdated treatments, which is often the case in completed classic RCTs. Finally, a valuable feature of the cmRCT design is the opportunity to evaluate and quantify the acceptance rates of the offered treatment (*ie,* SBRT). This offers new insights into patient preferences and reasons for refusal of SBRT. We feel that prevention of disappointment bias, more efficient and less selective patient recruitment, up-to-date standard of care, and quantifying patients' preference could significantly improve trials conducted according to the cmRCT design.

In conclusion, the VERTICAL study is a pragmatic randomized trial, following the cmRCT design, which compares stereotactic radiotherapy with standard radiotherapy in patients with spinal metastases in terms of pain response, with the ultimate goal to improve quality of life.

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ETHICS APPROVAL AND CONSENT TO PARTICPATE

Institutional review board approval was obtained separately for both the PRESENT cohort (particularly the cmRCT infrastructure) and the VERTICAL study from the ethical committee of the University Medical Center Utrecht (reference numbers 13-261 and 14-275, respectively). The PRESENT cohort is published under NCT02356497 and the VERTICAL study under NCT02364115 on ClinicalTrials.gov. Written informed consent is obtained from all participants.

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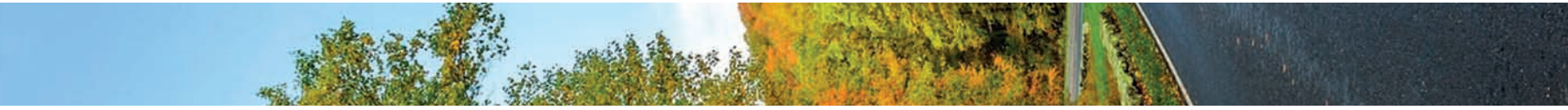

CHAPTER 9

The cohort multiple randomized controlled trial design: A valid and efficient alternative to pragmatic trials?

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ABSTRACT

Randomized controlled trials (RCTs)—the gold standard for evaluating the effects of medical interventions—are notoriously challenging in terms of logistics, planning and costs. The cohort multiple randomized controlled trial approach is designed to facilitate randomized trials for pragmatic evaluation of (new) interventions and is a promising variation from conventional pragmatic RCTs. In this paper, we evaluate methodological challenges of conducting an RCT within a cohort. We argue that equally valid results can be obtained from trials conducted within cohorts as from pragmatic RCTs. However, whether this design is more efficient compared with conducting a pragmatic RCT depends on the amount and nature of non-compliance in the intervention arm.

KEY MESSAGES

- The cohort multiple randomized controlled trial design was proposed as a variation of the pragmatic randomized controlled trial (RCT). A major difference between an RCT conducted within a cohort (cmRCT) and a pragmatic RCT is the timing of randomization relative to informed consent: in a cmRCT, only participants allocated to the intervention arm are asked for informed consent, which happens after they have been randomized to the intervention.
- Due to timing of the randomization, the non-compliance in the intervention arm may be higher in a cmRCT compared with an RCT. An increased rate of non-compliance in the intervention arm may be (partially) compensated for by lower (or even absent) non-compliance in the control arm. Non-compliance in the intervention arm can be accounted for by instrumental variable analysis.
- Participants allocated to the control arm of a cmRCT are unaware of being in the control group. This may reduce the risk of cross-over, drop-out and reporting bias. As compared with RCTs, standard of care applied in cmRCTs will better resemble routine care.
- More research is needed regarding generalizability of trial results, misclassification of the actual intervention status and implications of conducting multiple RCTs within a cohort.

INTRODUCTION

Randomized controlled trials (RCTs) are considered the gold standard for evaluating the effects of medical interventions. Pragmatic trials investigate the effectiveness of medical interventions or strategies under usual conditions [1, 2]. In contrast to explanatory trials, these trials are not placebo-controlled and typically do not blind the participants. Results of pragmatic trials often better reflect the effects to be expected in daily practice [2]. Both explanatory and pragmatic trials are notoriously challenging in terms of logistics, planning and costs. Less than one-third of RCTs achieve their planned recruitment target and follow-up is labour intensive [3, 4]. What is more, pragmatic RCTs, where participants are not blinded for the intervention status, may be complicated by response bias (also referred to as disappointment bias), and a considerable risk of noncompliance and cross-over between study arms [5, 6].

To overcome these challenges, the 'cohort multiple randomized controlled trial' design was proposed as a variation of pragmatic RCTs. [7] The basis of this design is a prospective cohort of participants with the condition of interest, receiving care as usual, who give informed consent for cohort participation. In our center, participants are furthermore asked for informed consent to be randomized in future RCTs conducted within the cohort. Participants are informed that they will be offered the experimental intervention if they are randomly selected. They are also informed that they otherwise might serve as controls without being notified and that their data can be used in a trial context [8]. For each participant in the cohort, clinical and patient-reported outcomes are captured at baseline and at regular intervals during follow-up. Within this cohort, multiple RCTs can be conducted. For this purpose, eligible participants who have provided the consent required for them to participate in an RCT within the cohort are identified. From this subcohort, a random selection of participants will be invited to undergo the experimental intervention. Eligible participants who were not randomly selected receive standard care, are not informed about the experimental intervention and serve as controls. Outcomes in this control group are compared with the outcomes of those who were offered the experimental intervention, in order to estimate the effect of the experimental intervention *vs.* usual care. Within the cohort, the same process can be repeated for trials of other interventions. The design appears especially attractive for clinical research areas where many interventions need evaluation, and for highly desired or expensive interventions [7].

The cohort multiple randomized controlled trial design is gaining interest in different fields of research [9-16]. Given the novelty of the design, several ethical and methodological aspects need in-depth evaluation. Ethical issues have been described elsewhere [8]. In this article we focus on the methodological issues of conducting one RCT within a cohort (cmRCT). We compare cmRCTs and pragmatic RCTs in terms of validity of the results and discuss approaches for analysis of a cmRCT.

VALIDITY OF CMRCT RESULTS

To obtain a valid estimate of the intervention effect, the group receiving the experimental intervention and the group receiving the standard intervention need to be comparable at the start of the study, during follow-up and at the end of the study [17]. However, at each of these moments, differences between cmRCTs and RCTs may occur.

At the start of the study: timing of randomization

Comparability of intervention groups at the start of the study is most effectively achieved by randomization. A major difference between a cmRCT and an RCT is the timing of randomization relative to the informed consent procedure. In an RCT, all participants are randomized after they have been informed about the intervention and after they consented to participate in the trial. In a cmRCT however, only participants allocated to the experimental intervention arm are informed about the intervention, but only after they have been randomized. Consent to participate is only sought from participants who are randomized to the experimental arm. This pre-randomization is different from, for example, the Zelen design. In the Zelen design, participants are randomized before seeking consent, [18] whereas participants in a cmRCT have given informed consent to be randomized, although the intervention is not known yet. Participants who are randomized to the experimental arm, may subsequently decline the experimental intervention (non-compliers). Here, the term non-compliance is used to indicate that participants who are allocated to one intervention arm decline that particular intervention at baseline. As a result, the proportion of non-compliance in the experimental arm is expected to be higher in a cmRCT compared with an RCT. This may particularly affect trials looking at interventions that are unpopular among participants, for example time-consuming or inconvenient interventions. In case of non-compliance, per protocol analysis may result in biased estimates of the intervention effect, if reasons for non-compliance are related to the outcome [19]. In RCTs testing an inconvenient, unpopular intervention, many participants will refuse to participate. Only a small subset of eligible participants may be willing to participate, possibly impairing generalizability. In a cmRCT, all eligible participants will be randomized, but participants allocated to the experimental intervention arm will be more likely to refuse the intervention. Hence, trial results will be generalizable to a broader population, but compared with an RCT, intention-to-treat (ITT) analysis will provide a more diluted estimate of the true intervention effect.

Challenges during follow-up

In a randomized double-blind placebo controlled-trial, blinding is relatively straightforward by using a placebo intervention for the control group. Because participants and their physicians are blinded, comparability of the intervention groups during follow-up is likely to be maintained. In contrast, pragmatic RCTs compare interventions under usual conditions, thus participants are not blinded and changes in, for example, health-related behaviour may differ between study arms [20]. Furthermore, participants may drop out if they are not allocated to the intervention they

had hoped for [21] or cross over to the preferred intervention arm, especially if the intervention is widely accessible to participants, such as exercise programmes. Participants in cmRCTs are not blinded, but participants in the control group are unaware of being in the control group of a specific trial. As a result, standard of care will not be affected by intervention allocation and will better resemble routine standard of care. Furthermore, drop-out rates may be lower in cmRCTs, since participants in the control group are not likely to withdraw from standard care. Moreover, information on baseline characteristics and outcome measurements (*ie,* the regular cohort measures) of drop-outs are still recorded, which is essential in the data analysis.

Measurement of endpoints

Ideally, the assessor of the outcome in trials is blinded for intervention status in order to prevent observer effects [17]. In pragmatic RCTs as well as in cmRCTs, participants are not blinded, which may lead to differential reporting of outcomes particularly in case of patient-reported outcomes. Some participants will consent to participate in a pragmatic RCT because they wish to receive the experimental intervention. They may be disappointed if allocated to the control arm and may subjectively report worse outcomes than were actually experienced, which may bias the observed differences in outcome between interventions [6, 12]. This is unlikely to happen among control participants in a cmRCT, since they do not know that they serve as control participants; this leaves potential bias in reported outcomes of patients in the experimental arm (*ie,* probably better outcomes than were experienced) only. Therefore in comparison with pragmatic RCTs, the potential for reporting bias may be reduced in cmRCTs.

ANALYSIS OF A CMRCT

The primary analysis in an RCT is typically an intention-to-treat (ITT) analysis, which maintains baseline comparability achieved by randomization [2]. Usually, in RCTs with blinded participants, compliance is high. In pragmatic trials, however, it is difficult and often undesirable to blind participants. This increases the risk of non-compliance, leading to underestimation of the true effect (*ie,* the effect that would be observed under perfect compliance) in ITT analysis. In pragmatic trials investigating the effects of an intervention under usual conditions, non-compliance can be seen as part of the intervention effect. However, researchers still might be interested in the 'explanatory' or 'real' effect of the intervention under perfect conditions. To control for non-compliance in RCTs, instrumental variable (IV) analysis (or Complier Average Causal Effect (CACE) analysis) may be used to account for non-compliance [19, 22, 23]. The IV analysis accounts for non-compliance by inflating the ITT effect to the effect that would be observed in the (possibly hypothetical) situation of perfect compliance. The estimated effect applies to those who comply with the offered intervention (Box 1).

IV analysis in an RCT

Consider an RCT with Z as randomisation assignment indicator (*eg*, intervention = 1, placebo = 0), X as actual intervention received (*eg*, intervention = 1, placebo = 0) and Y as outcome.

$$Z \rightarrow X \rightarrow Y$$

The ITT effect (*ie*, the average causal effect of Z on Y) differs from the average intervention effect of X on Y if some participants do not comply with the assigned intervention. The smaller the rate of compliance (*ie*, the smaller the relation between Z and X), the more the ITT effect and the average effect will tend to differ. To obtain the effect that would be observed under perfect compliance (IV effect), the ITT effect needs to be inflated. In IV analysis the average effect of X on Y is estimated from two effects of Z, namely the average effect of Z on Y and the average effect of Z on X in the following way:

$$\frac{Z \rightarrow Y \quad \textit{(ITT effect)}}{Z \rightarrow X \quad \textit{(compliance)}}$$

To obtain the average intervention effect, one inflates the ITT effect in the numerator of the estimator by dividing by a factor, which is lower as compliance decreases. The weaker the association between Z and X, the more the ITT effect will be inflated because of the shrinking denominator. If compliance is perfect (*ie*, Z equals X and Z à X = 1), the ITT effect equals the IV effect. Compliance (*ie*, Z à X) can be estimated as the difference in the observed probabilities of receiving the experimental intervention between the two allocation groups. IV analysis estimates the effect in those who comply with the allocated intervention.[22–24]

ITT versus IV analysis

In a cmRCT, the compliance in the control group (*ie,* usual care) will approximate to 100%, since participation in the cohort is conditional on receiving the standard of care. Since control participants are not informed about the experimental intervention, cross-over to the experimental intervention arm is unlikely. Compliance in the experimental intervention arm, however, may be substantially lower than 100%, since participants are free to accept or to decline the experimental intervention. To illustrate the impact of compliance, we compared ITT and IV analysis in both cmRCTs and RCTs. We considered a hypothetical randomized trial with two intervention arms, which is designed to detect a 10% difference in the risk of the outcome. The risk of the outcome is 10% in the experimental intervention arm, and 20% in the control arm. We simulated four approaches: (i) ITT analysis of an RCT; (ii) ITT analysis of a cmRCT; (iii) IV analysis of a RCT; and (iv) IV analysis of a cmRCT (Figure 1). In all four approaches, the true

intervention effect is observed when there is perfect compliance. In both RCTs and cmRCTs, the observed risk difference (obtained with ITT analysis) obviously depends on the proportion of non-compliance: the ITT estimate becomes more diluted as non-compliance increases. Since non-compliance occurs in the experimental intervention group only, the dilution is less in the cmRCT scenario, yielding a less biased estimate of the true treatment effect. Due to the timing of randomization in a cmRCT—consent to participate is sought after randomization—higher

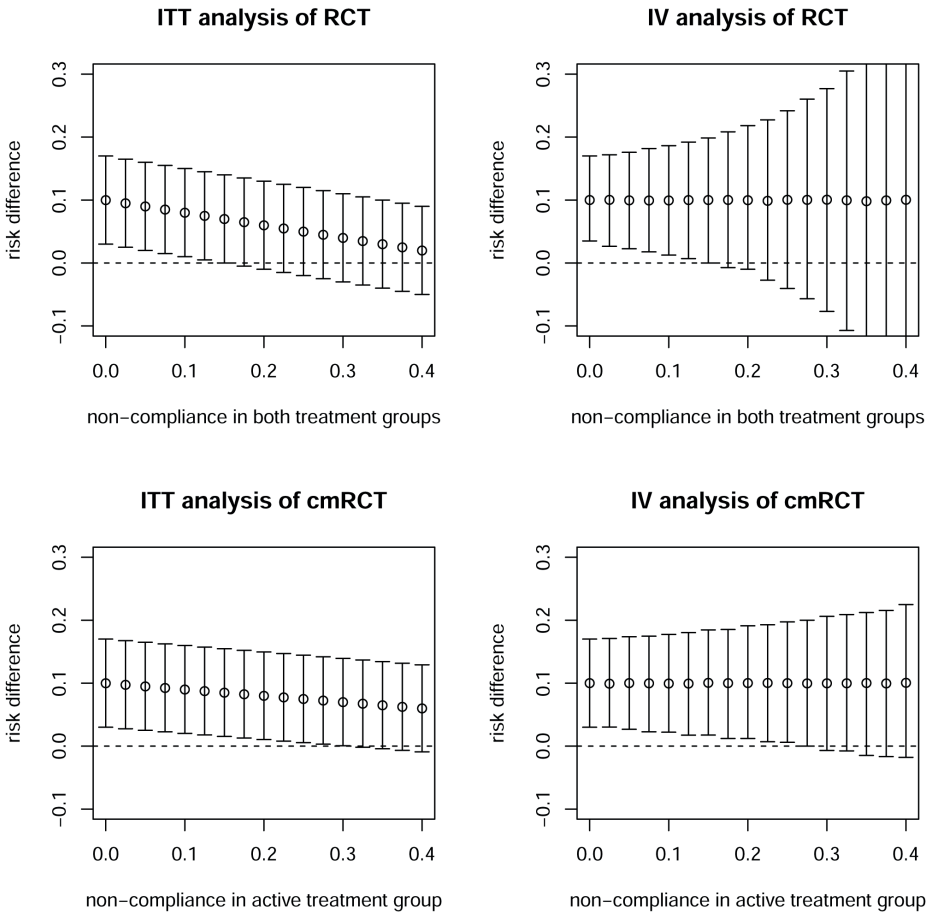

Figure 1. Numerical example of ITT analysis and IV analysis in both RCTs and cmRCT studies. Note that non-compliance in RCTs is possible in both intervention arms whereas, in cmRCT studies, non-compliance will be in the experimental treatment arm only. In a RCT at 10% non-compliance, there is 10% non-compliance in both arms, resulting in a 10% total non-compliance. This is in contrast to 10% non-compliance in a cmRCT, since non-compliance occurs in the experimental intervention arm only. This results in a 5% total non-compliance. Higher non-compliance is to be expected in the experimental intervention arm of the cmRCT. However, a cmRCT has room for more non-compliance in the experimental intervention group in comparison with an RCT in which non-compliance is expected in both intervention arms.

noncompliance is to be expected in the experimental arm of the cmRCT compared with the experimental arm of a pragmatic RCT. However, because of the high compliance in the control arm, a cmRCT has room for more non-compliance in the experimental arm in comparison with an RCT in which non-compliance is expected in both intervention arms (Figure 1a, b). Possibly there will be situations in which the amount of non-compliance in the experimental arm is too large to be compensated for by the low amount of non-compliance in the control arm. The intervention effect among compliers is estimated using the IV analysis, at the expense of precision. This imprecision increases more slowly in the cmRCT scenario since the probability of receiving the experimental intervention in the control group is very low and non-compliance is in the experimental intervention arm only. Note that at the same total amount of non-compliance—thus a double amount of non-compliance in the experimental intervention and zero non-compliance in the control arm—the results from a cmRCT are comparable to the results from an RCT (Figure 1c, d). Still, the main advantage of a cmRCT is the containment and control of the non- compliance, since all non-compliance accumulates in the experimental arm. Conducting a cmRCT, one should consider the amount of non-compliance to be expected in the

Assumptions of IV analysis

In RCTs, the indicator of (random) assignment of the intervention can be considered as an IV and thus used in IV analysis in order to estimate the average causal effect of the intervention. An IV should satisfy three key assumptions: the IV is predictive of actual intervention status, does not share common causes with the outcome and affects the outcome only through the intervention [22-24]. The first and second assumptions easily hold in RCTs and cmRCTs, since allocation of the intervention (*ie*, the IV) likely will be associated with actual intervention status, and by randomization assumption two is met as well. However, assumption three may be violated in pragmatic RCTs where participants are deliberately not blinded. In these cases, participants may change their behaviour when (not being) offered the intervention. Therefore, random allocation may affect the outcome via, for example, lifestyle changes as well as via the intervention. In a cmRCT however, participants allocated to the control group do not know that they serve as controls. Therefore, assumption three might be less violated in cmRCTs than in pragmatic RCTs.

DISCUSSION

In this paper, we compared cmRCTs with pragmatic RCTs and explored approaches to analyse cmRCT results. Participants in a cmRCT are recruited from an underlying cohort and outcomes measured in this cohort are relevant for the RCTs conducted within that cohort. Therefore, this design would be mostly applicable in cohorts specifically designed as cmRCT cohorts. Once such a cohort has been established, setting up trials will likely be less expensive and will require less effort compared with RCTs because a research infrastructure is already in place. Moreover,

the cohort allows for unequal randomization by making use of the (large) control group of the cohort. This may be especially attractive in the case of expensive experimental treatments, to reduce the costs of a trial. Another advantage of the cmRCT is that participants in the control group are unaware that they are participating as controls in a randomized trial. This will reduce not only the potential of reporting bias, but also cross-over of participants from control arm to experimental treatment arm.

Because of its design, cmRCTs are most suitable to evaluate experimental interventions that are not easily accessible for participants. If the intervention under study is in fact accessible to those in the control group (*ie,* usual care), compliance in that group may be less than 100% since participants may undergo the experimental treatment on their own initiative. For example, a cmRCT studying the relative effectiveness of two pharmacological drugs that are already on the market will face this challenge; yet this seems unlikely when comparing drugs in a pre-licensing stage. However, to emphasize again, one of the advantages of cmRCTs is that by not informing the control group, contamination may be limited.

So far, we (implicitly) discussed cmRCTs in the context of studies assessing superiority of one intervention over another. Alternatively, the aim of a trial might be to show non-inferiority or equivalence of two interventions. In non-inferiority and equivalence trials, an ITT analysis is anti-conservative, [25] particularly when non-compliance rates are high. IV analysis, as applied in the analysis of a cmRCT, may partly overcome this problem. Note that precision of IV estimates will be smaller (*ie,* wider confidence intervals) than the precision of estimates from an ITT analysis conducted in a study with full compliance.

Very few trials are purely explanatory or pragmatic; there is a continuum rather than dichotomy [2]. Different choices in design result in a more pragmatic or more explanatory trial, for example design choices described in the PRECIS-2 tool such as eligibility criteria, setting of a trial and follow-up [2]. In an RCT, randomization is the essential feature; all other design features are optional. The choices made regarding these other design options will make a trial more pragmatic or more explanatory. By design, the comparator in a cmRCT will always be care as usual, making use of existing staff and resources. This is extremely pragmatic in nature. Participants are recruited from an underlying cohort in which all participants with the condition of interest and receiving usual care are enrolled. It is considered very pragmatic to recruit patients in usual care without overt recruitment effort [2]. Moreover, the cmRCT participants recruited from a cohort may also better resemble the population of (future) users of the intervention under study, which again can be considered pragmatic [2]. However, more explanatory choices could be made as well. Very tight selection criteria could still be applied, resulting in a more explanatory cmRCT. The cohort provides regular outcome measurements but presumably more than are done in usual practice. Various adjustments to the intensity of these measurements will move

the trial toward the explanatory end of the continuum. Specific directions for administering the experimental intervention by practitioners deemed to have sufficient experience will also result in a more explanatory trial. Just like an RCT, a cmRCT will not automatically answer a purely pragmatic research question since several explanatory features may be included in the design. However, since the comparator will always be care as usual and participants are recruited from an underlying cohort, all cmRCTs are likely to be located at the pragmatic end of the pragmatic–explanatory continuum.

CONCLUSION

A major difference between an RCT and an RCT within a cohort (cmRCT) is the timing of randomization. Participants in an RCT are randomized to intervention arms after they consent to participation. This is in contrast to a cmRCT in which only participants allocated to the experimental arm are asked for consent to receive the intervention, and only after they have been randomized. Therefore, non-compliance in the experimental arm may be higher in a cmRCT compared with an RCT. On the other hand, control participants in a cmRCT do not know they are in the control arm, which will better mimic routine standard of care and lower the risk of loss to follow-up and response bias. Future studies implementing the cohort multiple randomized controlled trial design need to be conducted in order to quantify the magnitude of these phenomena. Based on our evaluation, we conclude that results from single cmRCTs are as valid as those from pragmatic RCTs. Whether the cohort multiple randomized controlled trial design is more efficient compared with pragmatic RCTs depends on the amount and nature of non-compliance.

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CHAPTER 10

Summary

Many patients with cancer develop bone metastases during the course of their disease. Because of improvements in systemic treatment options for the primary tumor, survival of patients suffering from bone metastases is improving substantially. The presence of metastatic bone disease is a poor prognostic sign with pain as an important symptom impacting on quality of life. For patients with painful bone metastases, radiotherapy is the standard local treatment. In this thesis, different aspect of the radiation treatment of patients with bone metastases are explored, working towards an individualized approach of these patients.

KEY POINTS

- The majority of patients with painful bone metastases experience pain relief after conventional radiotherapy.
- It is difficult to identify the patients who are unlikely to respond to palliative radiotherapy.
- The SINS is suitable for discriminating patients for referral to a radiation oncologist or an orthopedic surgeon, but it does not predict clinical outcomes.
- MRI is more reproducible than CT in delineation of bone metastases.
- The simultaneous integrated boost approach leads to better sparing of healthy bone and has the potential to reduce the risk of vertebral compression fractures.
- Stereotactic radiotherapy for bone metastases seem to result in higher pain response and local control rates, but this may very well be the result of study methodology and patient selection.
- The cmRCT design may improve trials by prevention of reporting bias, more efficient patient recruitment, quantification of patients' preference, and up-to-date standard of care, also in the palliative setting.
- Results from single trials conducted within cohorts are theoretically as valid as those from pragmatic, classic randomized controlled trials.

For patients with painful bone metastases, palliative conventional radiotherapy constitutes the standard of care. Its effectiveness has primarily been evaluated in trial populations. After enrollment of the first 500 PRESENT patients, we studied pain response to palliative radiotherapy in a prospective cohort of unselected patients with bone metastases in **Chapter 2.** The majority of patients (61%) experience pain relief after radiotherapy with a median time to response of 4 weeks. Of the patients who experienced pain relief, around two-third spend their remaining life with less pain without the need for retreatment. This means, however, that a large portion of patients does not respond to radiotherapy. New interventions or combination of conventional treatments for patients with symptomatic bone metastases are needed. Furthermore, it is important to identify those patients who are not likely to respond.

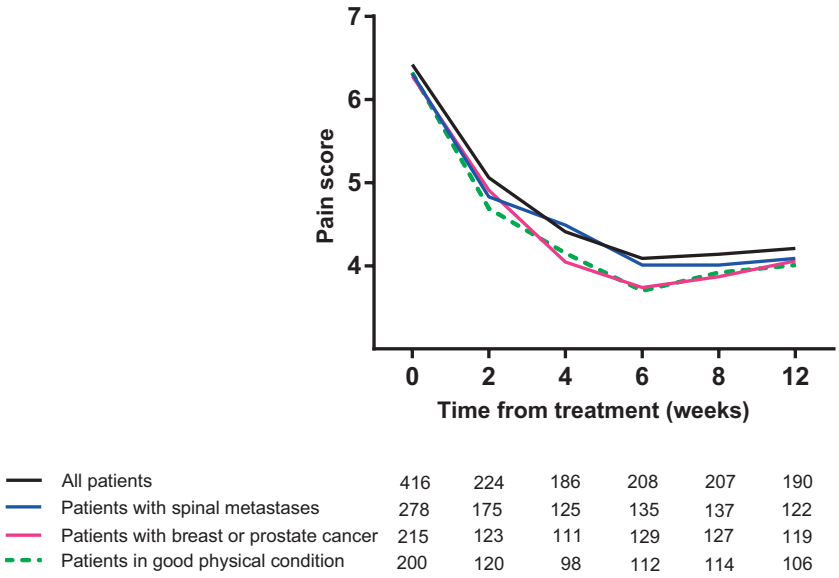

Figure 1. Pain scores during the first 3 months after treatment for all patients, patients with spinal metastases, patients with breast or prostate cancer, and patients in good clinical condition (*ie*, WHO score 0–1). Pain was scored on an 11-point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). The numbers below the graph indicate the number of patients that provided pain scores at specific time points.

In **Chapter 3,** we used the data of 965 patients with painful bone metastases who attended the palliative clinic of the Odette Cancer Centre in Toronto, Canada, to develop a prediction model to identify patients who are unlikely to respond to conventional radiotherapy. Primary tumor site, performance status, and baseline pain score are associated with pain response. The observed response rates after radiation therapy increased from 38% for patients with the highest risk score to 80% for patients with the lowest risk score and were in good agreement with the predicted response rates. However, with a corrected *c*-statistic of 0.63, the risk score is only modestly able to discriminate good and poor responders. Response rates after radiation therapy are suboptimal, and its prediction remains difficult, showing the need for new and better predictors.

Table 1. Risk score for response after palliative radiation therapy according to score categories

Factor	Contribution to risk score
Primary tumor	
Breast or prostate	0
Lung	7
Other	8
KPS	
80-100	0
50-70	6
20-40	12
Pain at baseline	0.7

Risk score	Predicted response
<6	76%
6-9	65%
10-13	54%
14-18	45%
>19	35%

Abbreviations: KPS, Karnofsky performance status. For a patient with primary prostate carcinoma, Karnofsky performance status of 70, and a pain score at baseline of 6, the final tally of the risk score would yield 10.2 (*ie*, prostate carcinoma = 0 points; KPS 50-70 = 6 points; pain score of 6 = 6 x 0.7), indicating a predicted pain response of approximately 54%.

A possible factor that could be predictive for pain response in patients with spinal metastases is the degree of spinal (in)stability. Spinal instability is hypothesized to lead to mechanical pain, which can be described as pain that is exacerbated by axial load, and typically inflicted by bending, standing, or walking. It might be that pain caused by mechanical instability is not well treated by radiotherapy compared with pain resulting from local tumor activity. The pain component caused by the local tumor should be treated adequately with radiotherapy, leaving pain caused by (gross) mechanical instability untreated. In patients with increasing spinal instability, radiotherapy might be less effective because of the presence of a larger contribution of the mechanical pain component. This hypothesis is supported in **Chapter 4** where we found an association between spinal stability – reflected by a Spinal Instability Neoplastic Score (SINS) lower than 7 – and a complete pain response after radiotherapy. No association could be determined between SINS and an overall pain response, which might indicate that this referral tool is not yet optimal for prediction of treatment outcome.

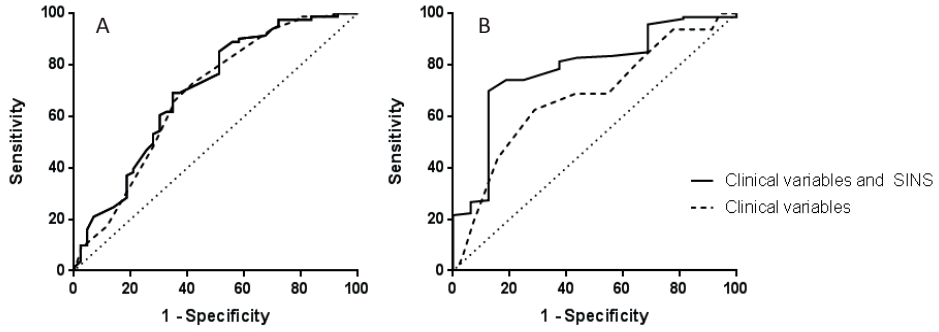

Figure 2. Receiver operating characteristics curves for the discriminative value of clinical variables (gender, primary tumor, and performance status, dotted line), and Spinal Instability Neoplastic Score in addition to those clinical variables (solid line) in predicting overall pain response (A) and complete pain response (B).

Conventional radiotherapy is thus the cornerstone in the management of bone metastases, but the use of Stereotactic Body Radiotherapy (SBRT) is increasing rapidly. SBRT promises better and longer duration of symptom relief together with improved local control and a potential for delayed disease progression. SBRT involves high precision, high dose delivery to the target volume while sparing healthy tissues. Accurate and consistent delineation of the target volume is therefore crucial in SBRT, for which knowledge of the inter-observer differences in tumor volume delineation is needed. For that purpose, five observers delineated 20 gross tumor volumes on CT, on CT co-registered with MR images and on MR images only in **Chapter 5.** Tumor delineation on MR imaging result in significantly larger mean volumes (46 cm^3) compared to CT–MRI (40 cm^3) and CT (35 cm^3). Considerable differences in interpretation of the tumor volumes are found, with the highest inter-observer agreement when delineated on MR images.

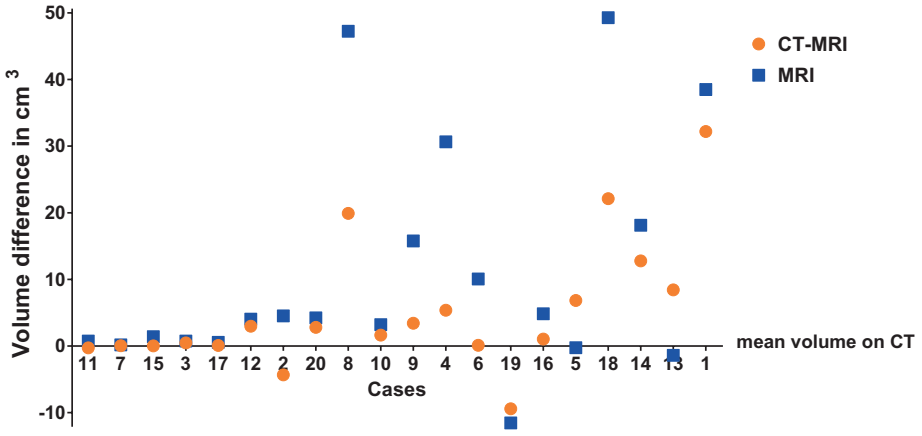

Figure 3. Absolute volume differences in cm^3 of GTV delineations, based on CT–MR and MR only compared to the mean volume of the lesion delineated on CT (X-axis), derived from contours of all observers. Cases are arranged from the smallest mean volume on CT (case 11: 1.2 cm^3) to the largest volume on CT (case 1: 184.7 cm^3). Cases 8 and 18: the volume difference on CT–MRI compared to CT only and MRI only compared to CT–MRI is similar. Case 5 and 13: the MRI volume mimics the CT volume, while on CT–MRI the volume increases in both cases. Case 19 is an outlier with the highest volume on CT imaging and a decrease in volume on CT–MRI and even more on MRI.

In spinal SBRT, concern has been raised about the risk of vertebral compression fractures, which have been reported to be as high as 40%. Prevention of these fractures is challenging because the metastatic lesion lies within the bone to be radiated. In **Chapter 6,** we propose a simultaneous integrated boost (SIB) approach designed to spare bone surrounding the metastasis to mitigate the risk of compression fractures. In this comparative planning study, both the SIB and non-SIB radiotherapy approach resulted in clinically acceptable and deliverable treatment plans. The bone surrounding the metastasis is substantially better spared in SIB SBRT plans: the median mean dose to the that volume was 12 Gy, while this was 17 Gy in the non-SIB SBRT plans. Organs at risk are easier spared in the SIB SBRT approach. In addition, the median coverage of the metastasis is higher in the SIB SBRT plans compared to the median coverage in the non-SIB SBRT plans. To see whether these differences are clinically relevant, we need follow-up data of patients who are treated with a SIB SBRT approach to confirm the hypothesis of less toxicity by sparing the surrounding relatively healthy bone.

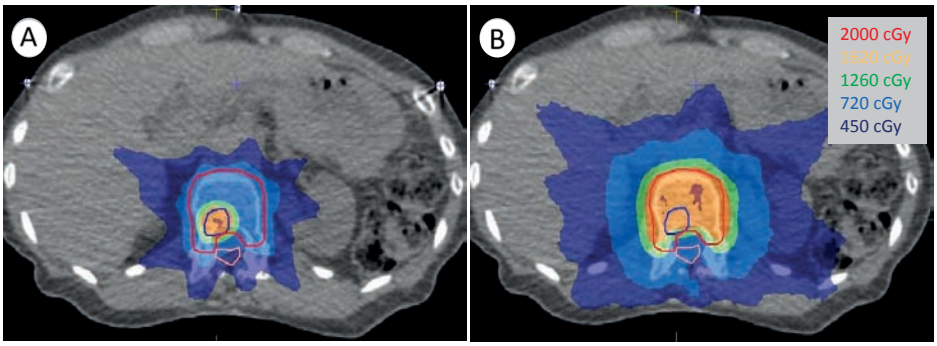

Figure 4. Delineation and planning for a representative case. (A) Axial plannings CT slice showing the simultaneous integrated boost (SIB) SBRT dose distribution for a small metastasis in the L1 lumbar vertebral body. (B) The non-SIB SBRT radiation treatment plan that this patient would have been given without the SIB SBRT approach. In this patient, the dose to the elective surrounding relatively healthy bone was effectively reduced from 18.4 Gy to 10.9 Gy.

To quantify pain response and local control following SBRT for bone metastases, we conducted a systematic review and meta-analysis in **Chapter 7.** Pooling the results of 29 articles – including 1865 patients – reporting on pain relief, overall pain response after SBRT for bone metastases is 81%. The pooled local control – from 40 studies including 3705 lesions – is 86%. Overall, SBRT for bone metastases is associated with higher rates of pain response than have previously been reported following conventional radiotherapy. Also, radiological local control rates seem excellent. These improved outcomes, however, may very well be the result of study methodology (*eg,* non-standard response assessments, not accounting for opioid use) and, more important, patient selection by selecting patients in a good physical condition with longer life expectancy. Large randomized trials are required to formally compare the impact of SBRT and conventional radiotherapy for bone metastases.

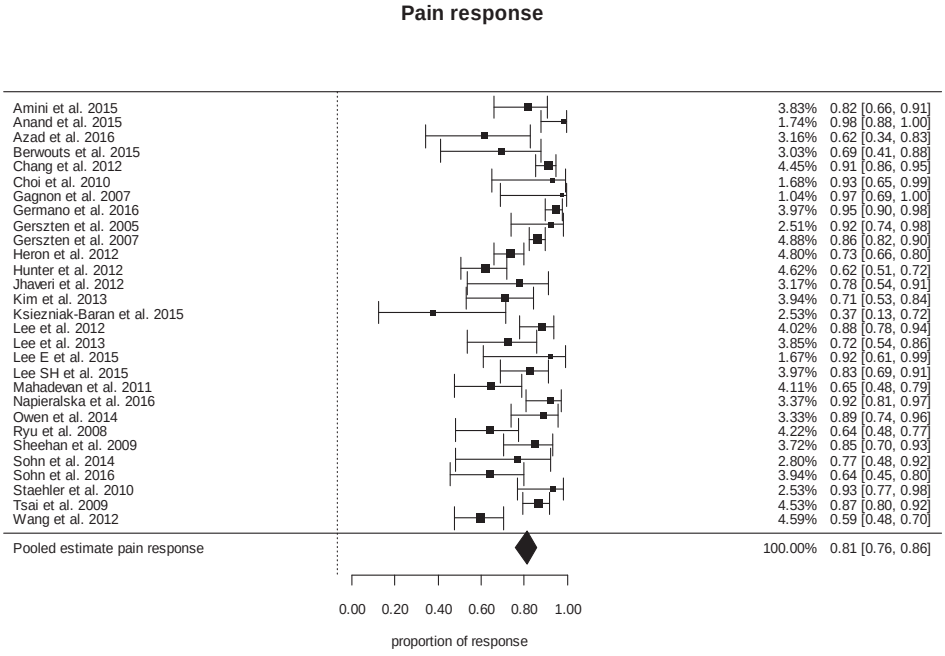

Figure 5. Meta-analysis of studies evaluating pain response after SBRT for bone metastases; values in parentheses are 95% confidence intervals

Due to the rapid pace of improvements in linear accelerator technology, SBRT is being increasingly adopted into daily clinical practice, so far thus without evidence from randomized trials. In **Chapter 8,** the first randomized study within the PRESENT cohort is presented: the VERTICAL trial. The VERTICAL trial aims to quantify the effect of SBRT in patients with bone metastases by following the 'cohort multiple Randomized Controlled Trial' design. In PRESENT, all patients with bone metastases referred for radiation therapy are enrolled. For each patient, relevant outcomes are captured at baseline and at regular intervals during follow-up. In addition, patients give informed consent to be offered experimental interventions. Within PRESENT, 110 patients are being identified as a sub cohort of eligible patients (*ie,* patients with unirradiated painful, uncomplicated bone metastases who are able to undergo stereotactic radiation therapy). From the sub cohort, a random selection of patients is offered SBRT (n = 55), which patients may accept or refuse. Only patients accepting SBRT sign informed consent for the VERTICAL trial. Non-selected patients receive standard radiotherapy, and are not aware of serving as controls. The cmRCT design addresses common difficulties associated with pragmatic randomized controlled trials, such as reporting bias in patients allocated to the control arm, slow recruitment, and poor generalizability.

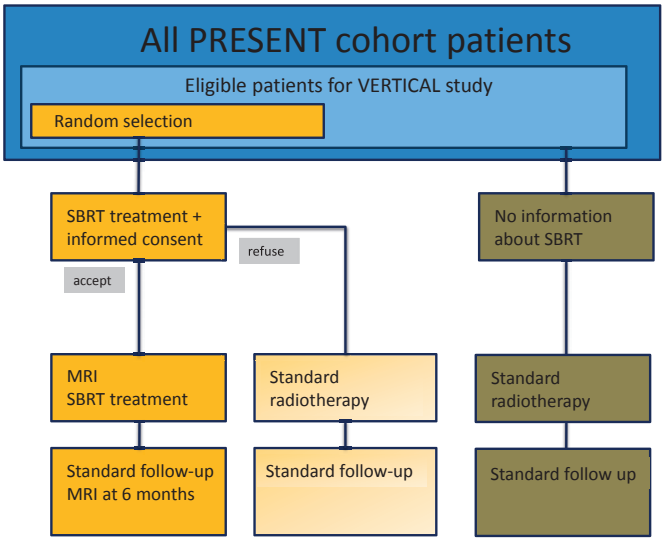

Figure 6. Study design VERTICAL study. A large observational cohort of patients with bone metastases is recruited and their outcomes regularly measured (dark blue box). Patients within the PRESENT cohort who meet the VERTICAL inclusion criteria are identified as a sub cohort of eligible patients (light blue box). Randomly selected patients (orange box) are offered the SBRT intervention. The outcomes of these randomly selected patients (*ie,* the intervention arm) are then compared with the outcomes of eligible patients not randomly selected who receive standard of care (*ie,* the control arm, brown boxes).

Randomized controlled trials (RCTs)—the gold standard for evaluating the effects of medical interventions—are notoriously challenging in terms of logistics, planning and costs. The cmRCT approach is designed to facilitate randomized trials for pragmatic evaluation of (new) interventions and is a promising variation from conventional pragmatic RCTs. In **Chapter 9,** we evaluated methodological challenges of conducting an RCT within a cohort. We argue that equally valid results can be obtained from trials conducted within cohorts as from pragmatic RCTs. Due to timing of the randomization, the non-compliance in the intervention arm may be higher in a cmRCT compared with an RCT. An increased rate of non-compliance in the intervention arm may be (partially) compensated for by lower (or even absent) non-compliance in the control arm. Participants allocated to the control arm of a cmRCT are unaware of being in the control group. This may reduce the risk of cross-over, drop-out and reporting bias. As compared with RCTs, standard of care applied in cmRCTs will better resemble routine care. However, whether this design is more efficient compared with conducting a pragmatic RCT depends on the amount and nature of non-compliance in the intervention arm.

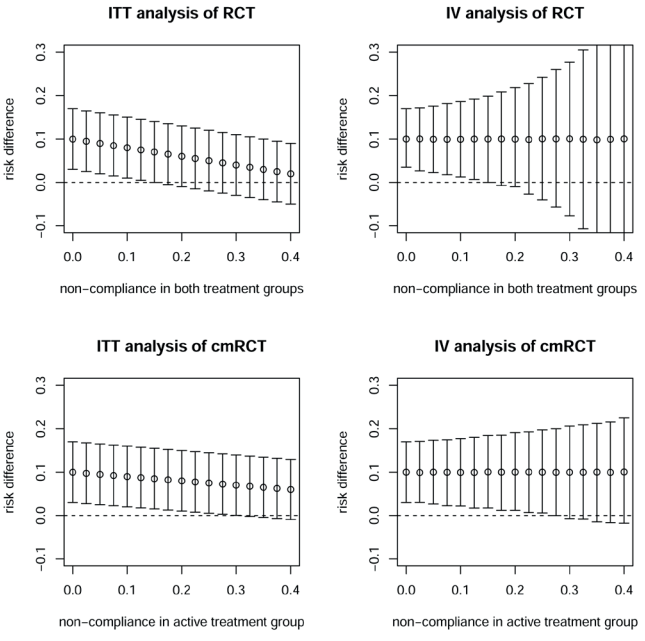

Figure 7. Numerical example of intention-to-treat analysis and instrumental variable-analysis in both RCTs and cmRCT studies. In a RCT at 10% non-compliance, there is 10% non-compliance in both arms, resulting in a 10% total non-compliance. This is in contrast to 10% non-compliance in a cmRCT, since non-compliance occurs in the experimental intervention arm only. This results in a 5% total non-compliance. Higher non-compliance is to be expected in the experimental intervention arm of the cmRCT. However, a cmRCT has room for more non-compliance in the experimental intervention group in comparison with an RCT in which non-compliance is expected in both intervention arms.

CHAPTER 11

General discussion

Medical science is applied science by definition: we aim at improving patients' survival and quality of life. This means we look at improving the treatments we have, and at giving the right treatment to the right patient. The other way around is equally applicable: medical practice should be research-based practice. What we offer as treatment should be the best known treatment, and we should aim to offer it to the right patients.

In this thesis, the goal is to improve existing treatment and apply best fitting treatments to patients suffering from bone metastases. Many patients with cancer develop bone metastases during the course of their disease. Patients with tumors that have metastasized to bone, are usually incurable: just 20 percent of patients with bone metastases is still alive at 2 years [1, 2]. Pain is an important symptom impacting severely on quality of life [3, 4] and is the main reason for referral to the radiation oncologist (*Chapter 2*). The group of patients with (symptomatic) bone metastases is large and radiation treatments for bone metastases account for more than 10% of all patients treated at our institution. For patients with painful bone metastases, palliative conventional radiotherapy, alone or in combination with other treatments, constitutes the standard of care for patients with painful bone metastases [5]. Trials conducted between 1986 and 2009 consistently showed pain response rates after conventional radiotherapy of approximately 60% [6, 7]. *Chapter 2* provides an update of the response rates that are obtained today, showing that pain response in our prospective cohort of patients with bone metastases is still around 60%. As pain relief lead to improvement in quality of life [8], the main challenge is to improve pain response in patients with bone metastases. While these patients generally cannot be cured, we try to improve the quality of their remaining life, resounding the extended summer days of an *Indian summer.*

THE IMPORTANCE OF SELECTING THE RIGHT TREATMENTS FOR THE RIGHT PATIENT

For treatments to be effective, the right patient should undergo the right treatments. For the majority of patients with bone metastases, radiotherapy is an effective treatment option. Even patients with a high probability of being a non-responder still have a 38% probability of response (*Chapter 3*). It is important that patients with painful bone metastases have access to radiotherapy. One way to improve access to radiotherapy could be that within existing multidisciplinary boards, patients with bone metastases are discussed. Within these boards, the optimal treatment option, including options such as stereotactic body radiotherapy (SBRT), surgical interventions, bone-targeting therapeutic radiopharmaceuticals, chemotherapy, immune therapy or a combination of these treatments, can be recommended to patients, where life expectancy and chance of response are important factors to consider. For radiation oncologists, to contribute to the discussion, it is helpful to know that primary tumor site, performance status, and baseline pain score are associated with pain response. Important to realize is that the risk score in *Chapter 3*

is not discriminative enough to offer patients at predicted high risk of non-response alternative treatments based on the risk score alone.

To improve treatment selection for patients with both spinal and non-spinal bone metastases, perhaps predictors such as serum or urine biomarkers could be added to existing prediction models with a view to improving accuracy. Bone metastases disrupt the normally tightly regulated process of bone resorption and formation. This disruption usually results in increased resorption and formation rates, which can be quantitatively measured by serum or urine biomarkers. Radiotherapy inhibits bone reabsorption, and thus osteoclast activity represented by bone turnover markers, thereby making bone turnover markers a potential future predictor for pain response. Several studies have demonstrated the use of urinary markers of osteoclast activity as a prognostic tool [9–11]. However, its use, and thereby benefit, in daily clinical practice might be limited by practical applicability. More apparent potential predictive factors might be parameters derived from staging and pre-treatment imaging. Positron emission tomography (PET) is increasingly being used for response evaluation after radiotherapy, especially in patients with oligometastatic disease. Metabolic activity of painful bone metastases, as measured on a PET scan, could be predictive for treatment response [12–14]. For diagnosis and monitoring of tumor response, conventional magnetic resonance imaging (MRI) is the most frequently used imaging modality [15]. Although several studies demonstrated the feasibility of using MRI to assess tumor response after conventional radiotherapy [16–18], only Switlyk *et al.* evaluated the predictive value of MR imaging findings for pain response in patients with bone metastases from breast cancer. They did not find an association between pain response after conventional radiotherapy and several imaging features [19]. However, they did not include advanced techniques such as diffusion weighted MRI and dynamic contrast-enhanced MRI into their assessment. Biological imaging features from PET and advanced MRI techniques might be helpful for making right treatment decisions and improving outcomes. However, these diagnostic imaging procedures are costly and (patients') time consuming, and before implementation can be pursued further research on costs *vs.* benefits is essential. According to the recently published Dutch treatment guideline for patients with spinal metastases [20], patients with a life expectancy more than 3 months who are fit to undergo surgery, the degree of mechanical instability of the spinal column is a critical factor in guiding treatment selection. Disruption of the homeostasis between osteoclasts and osteoblasts under the influence of tumor mediators can cause loss of mechanical integrity, leading to painful pathological motion within or between the vertebrae [21, 22]. Besides this painful effect, metastases may also cause pathological burst fractures [23]. Spinal instability is hypothesized to lead to mechanical pain, which can be described as pain that is dependent on position and activity, exacerbated by axial load, and typically inflicted by bending, standing, or walking [24]. It might be that pain caused by mechanical instability is not well treated by radiotherapy compared with pain resulting from local tumor activity (*eg,* direct invasion of tumor cells into healthy bone, periosteal stretching, or the release of inflammatory mediators) [25, 26].

The component caused by local tumor pain can be treated adequately with radiotherapy, leaving pain caused by (gross) mechanical instability untreated. With increasing spinal instability, radiotherapy might be less effective because of the presence of a larger contribution of the mechanical component to the perceived pain. This hypothesis is supported in *Chapter 4* where an association between spinal stability – reflected by a Spinal Instability Neoplastic Score (SINS) lower than 7 – and a complete pain response after radiotherapy was found. However, no relation could be found between the SINS and overall pain response (*ie*, both complete and partial response) to radiotherapy. In most spinal metastases patients with a partial response, both components of pain (*ie*, local and mechanical) are probably present simultaneously. The SINS is not a reliable tool to identify at baseline those patients who suffer disproportionally from mechanical pain, so that surgical intervention is justified. In addition, the SINS does not identify those patients that will deteriorate in terms of spinal alignment or develop a new pathologic fracture [27]. Maybe a more clinical definition of mechanical instability, with a focus on the characteristics of back pain, is needed.

As most patients will have a combination of both mechanical instability and local tumor activity, likely a proportion of these patients could benefit from a combination of these two treatment modalities. When radiotherapy and surgery are combined in the elective treatment of painful unstable spinal metastases, surgical stabilization is usually followed by postoperative conventional radiotherapy. Given the likely higher rates of wound complications following pre- or postoperative conventional radiotherapy, a minimum 1-week interval but preferably longer between surgery and radiotherapy is currently recommended [28]. With the advancement of precise radiotherapy planning and delivery techniques, radiation doses to the posterior surgical site including subcutaneous tissues can largely be reduced. This allows shortening of the interval between surgical stabilization and radiotherapy with both interventions being performed in a single, shorter hospital admission. Preliminary results of the BLEND trial, investigating the safety and feasibility of SBRT followed by surgical stabilization within 24 hours for the treatment of unstable spinal metastases, show no serious adverse events related to the combination of both treatments [29]. This optimization in timing of both treatments could advance the start of adjuvant systemic treatment if needed or interrupted and radiotherapy-induced tumor pain relief could be experienced earlier. Selected patients with both local and mechanical painful spinal metastases, are likely to benefit from the BLEND treatment approach. Within the PRESENT cohort, the outcomes of this approach will be further investigated.

Notably, some patients have multiple lesions that are not all painful, and not all patients with bone metastases experience pain. In a prospective study, bone pain was seen in only a third of patients with bone metastases [30]. Why do some bone metastases cause pain while others do not? Mapping the painful and the asymptomatic lesions may clarify what characteristics of painful lesions could be. This could provide further insight and guidance in selecting the right

treatment for a specific painful lesion. Within the PRESENT cohort, patients with bone metastases are followed prospectively by using Patient Reported Outcome Measures (PROMs) and survival. In addition, imaging data at baseline and during follow-up is collected and stored. In the future, these data can be used to investigate independent predictors and monitor patients that received (local) treatments with the aim to further select the right treatment for the right patient.

IMPROVEMENT OF TREATMENT

In trying to improve pain relief in patients with bone metastases, we need to continue to improve our treatment options. The VERTICAL trial, testing the hypothesis that escalating the dose to bone metastases improves pain response, is described in *Chapter 8*. The VERTICAL trial is conducted according to the cohort multiple Randomized Controlled Trial (cmRCT) concept and is therefore pragmatic by design. During the execution of this trial, several study amendments were necessary to continue keeping up with clinical practice. For example, instead of allowing the prescription of single fraction SBRT only, an amendment was approved by the Institutional Review and Ethics Board of the UMC Utrecht and subsequently implemented, allowing the prescription of an equivalent dose using other fractionation schedules – as is common in clinical practice. Reasons to fractionate radiation doses include close proximity of visible metastases to the spinal cord, or involvement of more than two consecutive spine segments. Furthermore, we extended the VERTICAL inclusion criteria to patients with non-spinal bone metastases as we expect SBRT will increasingly be delivered to patients with non-spinal bone metastases, particularly in the oligometastatic setting. A substantial amount of patients enrolled in VERTICAL dropped out for several reasons, including further deterioration of health or development of neurological/clinical symptoms during SBRT preparations. Probably, the *full* SBRT treatment, including a CT- and an MRI-scan in the treatment position while lying in a vacuum cushion is feasible for patients in good physical condition without pain. Such patients are often the ones with oligometastatic or low burden disease. However, patients for whom the VERTICAL trial was designed (*ie,* all patients with painful lesions in a reasonable physical condition) were not always able to undergo this treatment. These patients might benefit from *SBRT light*, in which for example the MRI in treatment position and thereby the SIB SBRT approach is omitted.

In addition to treatments being beneficial, treatment-induced risks should be minimal. For spinal metastases, concern has been raised about the occurrence of vertebral compression fractures (VCF) as a serious adverse event of SBRT [31]. Studies investigating SBRT-induced VCF rates showed crude risk rates ranges from 11% to 39% [32–35]; higher than those seen after conventional radiation (<5%) [7]. It is difficult to compare VCF rates after SBRT with rates after conventional radiotherapy and the risk after conventional radiotherapy, as the incidence of VCF after conventional radiotherapy is possibly underestimated, as most patients do not regularly

undergo imaging after conventional radiotherapy. Furthermore, not all VCF are symptomatic or need salvage treatment [33, 34].

Compression fractures might result from tumor-induced disruption of the homeostasis between osteoclasts and osteoblasts. However, there are two reasons why VCF might be the result of high dose radiotherapy. First, histopathological evidence of two cases of VCF after SBRT showed radiation-induced osteonecrosis, which was likely a causative factor in destabilizing the vertebrae resulting in VCFs [36]. From BLEND study patients, post-SBRT biopsies were obtained within 24 hours after single fraction SBRT of 18 Gy and showed that early effects of SBRT include vascular damage and increased apoptosis, desmoplasia and necrosis [37]. Osteoradionecrosis and tumornecrosis are therefore radiation effects, compromising the ability of the vertebrae to withstand the axial loading forces. This process might be comparable to the risk of tissue necrosis in brain radiosurgery, with the risk of necrosis increasing with a higher dose per fraction [38]. Second, several studies determined the risk of VCF in patients receiving high dose radiation for primary thoracic or abdominal tumors, without spinal metastases. Especially in high risk patients, vertebral fractures were associated with the radiation dose absorbed by the spine, as fractures were mostly seen in the high dose regions [39].

Prevention of VCFs is challenging because the metastatic lesions are situated within the segments at risk. Therefore, we implemented the simultaneous integrated boost (SIB) SBRT approach in our institution for treatment of spinal metastases aiming to mitigate the VCF risk by sparing the (relatively) healthy surrounding bone (*Chapter 6*). Although outcome data comparing differences in VCF risk and local control rates between SIB and non-SIB SBRT are lacking, there are several reasons to continue with this approach. First, from *Chapter 6* it is learned that SIB SBRT treatment plans are clinically acceptable and deliverable. What is more, we were able to better spare organs at risk, especially the non-tumorous bony compartment surrounding the tumor, the nerve roots and spinal cord. Additionally, the coverage of the metastasis itself is better in the SIB SBRT plans. A possibly reason to abandon the SIB SBRT approach comes from *Chapter* 5, in which it is seen that the gross tumor volume (GTV) of bony metastases is not easily contoured as there is large inter-observer variability. Increasing the precision of GTV delineation may come at the cost of an increased risk of missing clinically relevant and symptomatic disease.

Yet, there is essential information missing in order to make a final decision whether to continue or abandon this SIB SBRT approach for spinal metastases. In *Chapter 5* it was shown that tumor delineation on MR imaging resulted in significantly larger mean volumes compared to CT. We need to investigate how accurate all tumorous areas are seen on imaging. This requires large-scale clinical research and possibly pathologic validation analyses. High quality follow-up data are needed, preferably including MR imaging in addition to functional imaging. Using these data, VCF and local control rates can be compared after both SIB and non-SIB SBRT

thereby determining the pattern of recurrence, including the amount of in-field, marginal and out-of-field recurrences. Possibly, only for metastases that are well defined, the spinal SIB SBRT approach is feasible and justifiable. Well defined lesions are generally osteolytic. Given that the presence of an osteolytic metastatic lesion is one of the most consistent and important predictors of developing VCF, vertebral bodies harboring osteolytic lesions may possibly the ones for which a SIB approach is most beneficial [31]. Conversely, as surgical stabilization techniques become less invasive, it could become an option to operate patients with the highest risk of compression fractures. Likely, there is overlap between this group of patients and those patients with unstable spinal lesions benefitting from the BLEND approach.

To SIB or not to SIB is different question for non-spinal bone metastases, as we cannot irradiate an entire non-spinal bone with high dose radiotherapy. However, while the clinical target volume (CTV) for spinal metastases is clearly defined [40], the CTV is not well established in non-spinal bony lesions. Recently, the pattern of recurrence after SBRT for pelvic bone metastases was evaluated [41]. In this study, a margin of 5 to 10 mm was added to the GTV to create the CTV. Still, in 7 out of the 17 included patients, marginal and out-of-field recurrences were observed with an average distance of more than 30 mm from the initial metastasis. The authors hypothesized that dissemination inside the pelvic bone caused out-of-field recurrences. A small study from our department showed that contouring of bone metastases from renal cell carcinoma on MR imaging resulted in clinically relevant and statistically significant larger volumes (mean increase of 41%) compared with computed tomography (CT) imaging [42]. In short, also for non-spinal bone metastases, to reach high local control rates, large-scale clinical research validating high quality (MR) imaging with pathologic outcomes are needed to determine the extent of the CTV that should be added to the GTV.

As SBRT claims to achieve higher local control rates, it is essential to know what local control looks like. The RECIST guideline is of limited use for classifying the response after SBRT as bone metastases are only deemed measurable if soft-tissue extensions of 10 mm or larger can be identified [43]. Blastic bone lesions are regarded non-measurable [43]. The MD Anderson Cancer Center criteria for response [44] are more applicable, although these remain of greater relevance in lytic lesions. Ultimately, validated response criteria are needed to assess tumor response after SBRT. For serial tumor response assessment, MR imaging is the most applied diagnostic imaging tool. Caveats in anatomic MR response imaging are pseudo-progression (*ie,* post-treatment fibrosis being mistaken for disease progression) and necrosis, as neither is observed with conventional radiotherapy and, as a result, might impair correct interpretation of images [15]. Research into functional MRI-based assessment of tumor response after SBRT for bone metastases is limited and needs further study. These functional imaging data might in turn be used in contour guidelines, thereby improving the irradiation of all tumorous areas leading to better local control.

Finally, it might be that dose escalation is not the most important step in improving response to radiotherapy as a radiation dose-response relationship for doses above 8 Gy has not been established [6, 7]. However, three randomized trials concluded that a single fraction of 4 Gy is less effective than 8 Gy, suggesting a dose-response relationship for single fractions below 8 Gy [45–47]. If there is indeed a threshold dose below which pain relief is less likely and of slower onset, it may be important to ensure that the vertebral metastasis receives the intended dose. Most bone metastases are treated with conventionally planned radiotherapy techniques [48]. The drawbacks of this approach are that the dose is not specifically delivered to the target and the irradiation of large volumes of normal tissues. Using more advanced planning techniques, such as IMRT, ensures the radiation oncologist of delivering at least enough dose to the bony lesion. Furthermore, it is hypothesized that reducing the dose to normal tissues might improve overall pain response [49] which could be an additional benefit of the SIB SBRT approach. If doses to normal tissues should be reduced and radiation dose should precisely hit the target, it is of increasing importance to correctly identify the target lesion. In this process, the MR-Linac (named Unity), developed in our department in close collaboration with Elekta AB (Sweden) and Philips (The Netherlands), might play a role as this systems combines 1.5 Tesla, diagnostic image quality MR images with a linear accelerator [50, 51]. The combination of anatomic information of the treated patient and online planning facility could eventually lead to a kind of One-Stop-SBRT for patients with bone metastases.

The challenges in evaluating pain response

In both patient (or treatment) selection and treatment improvement, it is important that treatment outcomes are evaluated accurately. The impact of treatment fractionation of conventional palliative radiotherapy on pain control in patients with bone metastases has been the focus of extensive international study [6, 7]. Thanks to these studies, the need to ensure comparable outcome reporting was recognized and led to the collaborative development and publication of International Consensus guidelines for the reporting of outcomes [48, 52].

Still, assessment of pain associated with bone metastases has many challenges. The consensus guideline suggests using a scale ranging from 0 to 10 – with 0 representing no pain and 10 representing maximal pain. It is difficult to choose the right timing for the assessment of pain. *Chapter 2* shows that for PRESENT patients, the median time to response was 4 weeks with a wide range up to 15 weeks. Not surprisingly, the importance of the length of the time frame in which pain response is measured is shown as well with a higher response rate after longer time intervals. For SBRT, the most common time point at which pain response is measured is 3 months post-treatment in order to capture all patients that show a response to SBRT. However, this time point might be too late for the measurement of pain response after conventional radiotherapy, as around 30% of the PRESENT patients died within 3 months. To minimize the confounding effect of attrition and additional treatments after radiotherapy (*eg,* the start of chemotherapy or

bisphosphonates), the consensus guideline for reporting outcomes should provide a suggestion to measure pain response in the period up to eight weeks after treatment. For SBRT, the measurement of pain response at 12 weeks is acceptable, as these patients generally are in a better physical condition with less risk of questionnaire fatigue due to shifting priorities, and less risk of dying within three months.

As radiotherapy is a local treatment modality, ideally the response at the treatment lesion is measured. However, it is difficult for patients with multiple lesions to distinguish between painful lesions. It is possible that radiotherapy was successful for one lesion, but not for another. In fact, the treatment to the treated lesion might have unmasked other lesions appearing more symptomatic post-treatment. Analgesic use poses a challenge in pain response assessment, in particular when analgesic doses are increased because of other lesions becoming symptomatic. With regard to pain medication, for response calculation to be in accordance with the international consensus guidelines, data on pain scores and opioid use only are needed [48]. In our cohort, we found that more than 30% of the patients used corticosteroids during radiotherapy. Corticosteroids could also have a beneficial effect on pain [53]. Furthermore, some patients not only have painful lesions but are also suffering from neurological complaints. In our cohort, around 40% of these patients used tricyclic antidepressants or antiepileptic drugs for pain of neurological origin. When calculating response rates, changes in the use of corticosteroid, tricyclic antidepressants or antiepileptic drugs are not taken into account. According to the consensus, patients with a 25% decrease morphine use were considered as responders. It is possible that patients using corticosteroids or neurological drugs also had reduced drug use as result of response after radiotherapy but were not regarded as responders since these drugs were not taken into account. To obtain a more realistic estimation of the radiotherapy effect, a broader range of relevant pain medication should be included in the consensus guideline.

According to the international consensus guidelines, patient response is captured as complete or partial but valuable information is lost when pain response is reported in this way: patients with a major response are not distinguishable from patients with a minor response. This information could be contributing in identifying predictive factors for response. For example, if hypothesis of tumor *vs.* mechanical pain is true indeed, it would be expected that patients with pain largely due to mechanical instability experience a minor response, while patients with tumor-induced pain should benefit more from radiotherapy. To evaluate whether this classification is relevant to patients, several cut-off points for major response (*eg,* major response could be defined as a decrease in pain score of at least 4 points and/or a decrease in analgesic use of at least 50%) could be tested in such a way that having a major or minor response is correlated with quality of life domains.

The systematic review discussed in *Chapter 7* demonstrates that despite the updated international consensus guidelines, fundamental differences still exist from study to study and adherence to the pain reporting guidelines in the SBRT papers is disappointingly low. *Chapters 2 and* 7 also show large differences between the response rates of the total treated population and the assessable patients: response rates are higher if only rates from assessable patients are reported. What is more, in most studies it is unclear whether assessable or total treated proportions was reported; both are necessary in this fragile patient population where survival is limited.

THE NEED FOR INNOVATIVE TRIAL DESIGNS

Where the right patient should be selected to undergo the right treatment, and researchers should aim at improving those treatments, it is important that theoretical benefits risk scores and new treatments are properly evaluated and proven by choosing the right methodology.

Patients experiencing pain relief have better quality of life compared with patients without response to radiotherapy [8]. It is therefore important to try to improve the response rate after radiotherapy. As we have seen in *Chapter 7*, SBRT seems to hold the potential to improve outcomes. Due to the rapid pace of improvements in linear accelerator technology, SBRT is being increasingly adopted into daily clinical practice [54], so far without evidence from randomized trials. High rates of pain and local tumor control for bone metastases treated with SBRT have been shown in *Chapter 7* and suggest better efficacy than conventional radiotherapy. However, patients included in the phase II trials who underwent SBRT generally had longer median survival compared to, for example, our PRESENT patients. As the key predictors for survival (*ie*, performance status and primary tumor [55]) are also independent predictors for pain response (*Chapter 3*), the favorable outcomes after SBRT demonstrated in *Chapter 7* may very well be the result of case selection. The potential superiority of SBRT for bone metastases in providing pain relief and local control still needs to be demonstrated within large randomized trials. In *Chapter 8,* we describe the pragmatic VERTCIAL trial according to the cmRCT design [56, 57]. There were several reasons to choose to set up the VERTICAL trial according to the cmRCT design. Many oncology clinical trials are never completed because they do not recruit sufficient number of patients to meet the scientific aims [58]. These unfinished trials represent inefficient use of resources both in terms of money and, more important, in patient time. More specifically, trials with low accrual have been shown to be more likely to evaluate radiation therapy (32% *vs.* 20% of trials with successful accrual) and be conducted in metastatic settings (odds ratio of 1.46 compared to non-metastatic studies) [59]. For the VERTICAL trial both risk factors (*i.e*, radiotherapy trial and trial in metastatic setting) are present. Indeed, in our center, two classic Randomized controlled trials (RCTs) recruiting patients with bone metastases had much longer inclusion periods than originally scheduled [60]. During the planned inclusion period, only approximately 15% of the eligible patient population was included. As stated in *Chapter 8,* we hope

to improve recruitment using the cmRCT design for the VERTICAL trial. Another potential methodological advantage of cmRCT is explored in *Chapter 9:* control participants in a cmRCT do not know they serve as control patients. This will better mimic routine standard of care and lower the risk of drop-out, cross over, and disappointment bias. The cmRCT design has the advantage that experimental interventions are compared with the most up-to-date standard of care. Furthermore, the cmRCT cohort offers an infrastructure which allows the simultaneously conduct of randomized trials.

Patients within the PRESENT cohort eligible to participate in the VERTICAL trial and allocated to the experimental arm, are free to accept or decline the offer of SBRT. This process will provide insight into patient preferences and reasons for refusal of SBRT. The cmRCT design is also more efficient for investigators since control patients do not need to be provided with information about the experimental treatment. Patients not eligible for the VERTICAL or patients who dropped out are more easily identified, and they will still be followed and outcome date will therefore be available. Very importantly, all referred patients with bone metastases are eligible for inclusion in the PRESENT cohort, and all patients receive study information by the research team before they see the radiation oncologist. After informed consent, patients can make the decision to join the PRESENT cohort or decline participation. In addition, patients who join the PRESENT cohort may give broad consent to be randomized to experimental interventions in the (near) future. This improves patients' autonomy and trial access without the judgment of their treating physicians interfering.

By using the cmRCT design, the hypothesis that SBRT achieves higher radiological local control rates, cannot be tested as patients in the control arm do not routinely undergo MR imaging during follow-up. Only clinical local control, for example pain control and the occurrence of adverse events, can be compared between the SBRT and control group. To test the theoretical advantage of applying ablative radiation doses for radiological local control, the classic RCTs of the RTOG group [61] and the RACOST trial [62] will provide answers and establish the clinical relevance of this endpoint. Because of their physical condition or changing priorities, patients selected for the intervention arm might not accept the offer of receiving SBRT. To compensate for non-compliance, in *Chapter 9* we see that instrumental variable analysis might be a valuable addition to intention-to-treat analyses albeit with loss of power. Whether the cmRCT design is more efficient compared with classic pragmatic RCTs depends on the amount and nature of non-compliance. Valuable insights on the yet theoretical benefits of the cmRCT design will be provided when the results of the RACOST trial and the VERTICAL trial are to be compared.

Originally, patients with oligometastatic disease were eligible for inclusion into the VERTICAL trial. Oligometastatic disease is considered an intermediate metastatic state, in which cancer exists as a limited number of metastases, before tumor cells acquire the ability to metastasize

grow more widely. These patients were however excluded from the VERTICAL trial, because radiation oncologists and referring physicians generally believe patients with three or less bone metastases should be treated with SBRT in order to prolong progression free survival.

Most clinical data supporting the use of SBRT in patient with oligometastases rely on non-controlled observational data. In light of these encouraging data, to withhold the individual patients with oligometastatic disease from SBRT treatment seems unethical. Although these results might seem favorable, observational data can lead to erroneous conclusions. One could argue that exposure of patients to SBRT, a treatment which also introduces increased SBRT-related risks (for example VCFs), can be considered unethical as well without solid level 1 evidence demonstrating clear benefits. As the VERTICAL trial does not include patients with oligometastatic disease, validity of the trial will not be violated, since the primary goal is to determine whether dose escalation per fraction will increase pain response, not progression free survival. As patients with oligometastatic disease, generally representing a cohort of patients in better physical condition, they will have a higherchance of response (*Chapter 3)*. As such, the results of the VERTICAL trial will not be generalizable to this patient population. As the PRESENT cohort was already recruiting patients before SBRT was introduced in our department, we are able to compare patients with oligometastatic disease treated before (*ie,* historic controls) and after the introduction of SBRT. In addition, it is of paramount importance to include all patients with oligometastatic disease into a nationwide registry. It is likely that patients considered to have oligometastatic disease harbor yet undetectable (micro-)metastases. Using observational data, predictive and prognostic factors can be identified to select patients who will develop more metastases shortly after treatment.

Ideally, all patients with bone metastases, regardless of the extent of their metastatic disease should be included in observational cohorts. Patient reported outcomes collected for research purposes could be in integrated into routine clinical practice thereby optimizing clinical care. For example, PRESENT patients indicating high pain scores after treatment, could be identified and approached by their radiation oncologist for re-irradiation. By reusing research data for clinical purposes, patients will be encouraged to complete questionnaires since they could be benefit directly, which simultaneously improves the quality of research data. These data, obtained to support clinical follow-up, can be used to facilitate future clinical trials using a cmRCT design.

Finally, also studies included in this thesis considered patients with bone metastases as a large, heterogeneous group with many tumor histologies. Significant differences in terms of histology and the effect of systemic treatments available for patients with primary tumors exist. Furthermore, patients differ with regard to localization, number of lesions, and physical condition. For example, the standard 8 Gy radiation dose to metastatic sites might be too high for fast-growing tumors possibly inducing inflammation and counteracting the pain-killing effect of the radia-

tion (*Chapter 3*). For patients with painful lytic lesion in the acetabulum, a higher dose may be necessary to induce remineralization leading to patients obtaining the ability to walk again. If we continue to considering all patients with bone metastases to be equal, we will not achieve optimal treatment selection. It is important to define what would be the best outcome for an individual patient. For the patients in a (possibly) truly oligometastatic state improved local control after SBRT and increased overall survival would be the ultimate goal. For the patient with an extensive burden of disease from a non-favorable tumor, optimal pain relief should be the focus. For some patients, the goal is to have an *Indian summer*, for other patients the goal is to live longer many seasons beyond that.

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ADDENDA

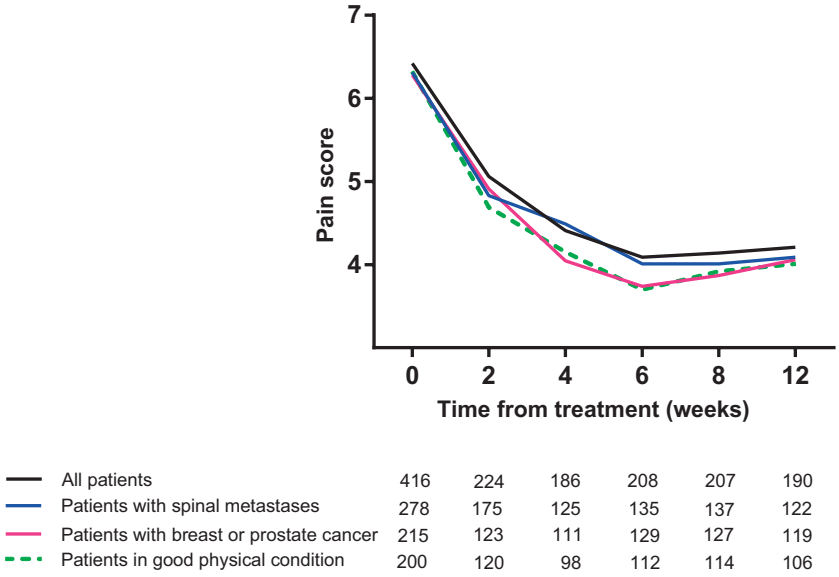
OP WEG NAAR EEN OP HET INDIVIDU GERICHTE BEHANDELING VOOR PATIËNTEN MET BOTMETASTASEN

Bij veel patiënten met kanker zaait de ziekte uiteindelijk uit naar de botten. Omdat de behandeling van kanker steeds beter wordt, wordt de groep van patiënten met botmetastasen steeds groter en leeft deze groep ook langer. Ondanks dat de behandeling van kanker beter wordt, is uitgezaaide kanker in het algemeen ongeneeslijk. Botmetastasen kunnen veel pijn veroorzaken, waardoor de kwaliteit van leven van patiënten lager is vergeleken met die van de algemene bevolking. De standaardbehandeling van patiënten met pijnlijke botmetastasen is radiotherapie. In dit proefschrift worden verschillende aspecten van de radiotherapeutische behandeling van patiënten met botmetastasen onderzocht met uiteindelijk als doel de individuele patiënt een behandeling op maat te geven.

BELANGRIJKSTE CONCLUSIES

- De meerderheid van de patiënten met pijnlijke botmetastasen heeft minder pijn na conventionele bestraling.
- Het is moeilijk om te voorspellen welke patiënten zullen reageren op radiotherapie, en welke patiënten pijn blijven houden.
- De SINS kan worden gebruikt om een onderscheid te maken tussen patiënten die verwezen moeten worden naar de radiotherapeut of naar de orthopeed, maar kan de pijnrespons niet voorspellen.
- MRI zorgt voor reproduceerbaarder intekeningen van botmetastasen in vergelijking met CT scans.
- In bestralingsplannen waarin alleen de tumor een hoge boost krijgt, wordt het gezonde omliggende bot goed gespaard, wat ervoor zou kunnen zorgen dat er minder compressiefracturen optreden.
- Stereotactische radiotherapie lijkt beter te zijn dan conventionele bestraling, maar dit beeld is waarschijnlijk het gevolg van slechte studieopzetten en selectie van de ´goede´ patiënten.
- Het cmRCT design kan, ook in de palliatieve oncologische setting, ervoor zorgen dat gerandomiseerde onderzoeken beter worden doordat er minder teleurgestelde patiënten worden geïncludeerd, inclusie efficiënter lijkt, en de standaardzorg altijd up-to-date is.
- Resultaten van een gerandomiseerd onderzoek uitgevoerd binnen een cohort zijn theoretisch even valide als resultaten van een klassieke RCT.

De standaard lokale behandeling voor pijnlijke botmetastasen is conventionele palliatieve bestraling. De effectiviteit van deze behandeling is vooral bekend uit gerandomiseerde onderzoeken, waarin een selecte patiëntengroep wordt onderzocht. In het in Utrecht opgerichte PRESENT cohort worden alle patiënten met botmetastasen, die naar de afdeling radiotherapie of orthopedie worden verwezen, geïncludeerd en vervolgens prospectief gevolgd. We onderzochten in **hoofdstuk 2** wat de pijnrespons is met behulp van de data van deze ongeselecteerde patiënten. De meerderheid van de patiënten (61%) ervaart verlichting van de pijn en de helft van die patiënten ervaart pijnverlichting binnen 4 weken. Dit betekent ook dat er ook veel patiënten geen effect merken van de bestraling. Nieuwe behandeling of nieuwe combinaties van al bestaande behandelingen voor patiënten met botmetastasen zijn dus nodig. Daarnaast is het ook belangrijk om patiënten te identificeren die geen effect zullen hebben van bestraling.



Figuur 1. Pijn scores van alle patiënten, patiënten met wervelmetastasen, met borst- of prostaatkanker, en van patiënten in een goede conditie tijdens de eerste 3 maanden na bestraling. Pijn werd gescoord op een schaal van 0 (geen pijn) tot 10 (ergst denkbare pijn). De getallen onder de grafiek geven weer hoeveel patiënten op dat moment een pijnscore hebben doorgegeven.

In **hoofdstuk 3** hebben we, gebruik makend van de data van 965 patiënten met pijnlijke botmetastasen die behandeld zijn in het *Odette Cancer Centre* in Toronto, Canada, een model gemaakt om te proberen te voorspellen welke patiënten baat hebben bij bestraling. Primaire tumor, conditie, en baseline pijnscores zijn geassocieerd met de respons na radiotherapie. Van de patiënten die de grootste kans hadden om niet te reageren op radiotherapie had 38% minder pijn na bestraling. Tachtig procent van de patiënten met de grootste kans wel te reageren had ook minder pijn na de bestraling. De voorspelde en daadwerkelijk geobserveerde percentages kwamen goed overeen. Helaas kan het model maar matig goed onderscheid maken tussen een patiënt die wel zal reageren en een patiënt pijn blijft houden (namelijk, van de 100 voorspellingen van pijnrespons bij een willekeurig paar patiënten, van wie 1 wel en 1 niet zal reageren, zijn er maar 63 voorspellingen goed). Responspercentages zijn dus nog niet optimaal, en het blijft moeilijk de respons te voorspellen. Daarom zijn er betere voorspellers nodig.

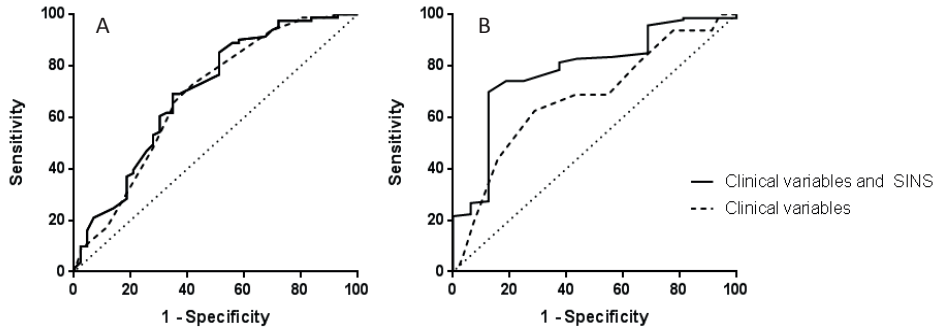
Tabel 1 Risicoscore voor pijnrespons na radiotherapie van pijnlijke botmetastasen

Factor	Bijdrage aan risk score
Primaire tumor	
Borst of prostaat	0
Long	7
Andere tumoren	8
KPS	
80-100	0
50-70	6
20-40	12
Pijn op baseline	0.7

Risicoscore	Voorspelde respons
<6	76%
6-9	65%
10-13	54%
14-18	45%
>19	35%

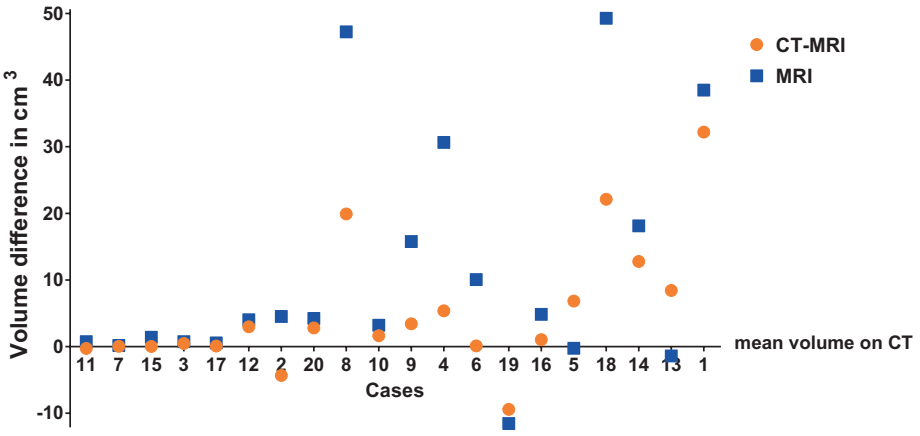
Afkortingen: KPS, Karnofsky performance status. Voor een patiënt met botmetastasen van prostaatkanker, een KPS van 70, en een pijnscore op baseline van 6, is de totale score is 10.2 (namelijk prostaatkanker = 0 punten; KPS 50-70 = 6 punten; en een pijnscore van 6 is 6 x 0.7), wat neerkomt op een voorspelde pijnrespons van 54%.

Een mogelijke voorspeller van pijnrespons voor patiënten met metastasen in de wervels is de (in) stabiliteit van de wervelkolom. Door de uitzaaiingen in de wervelkolom kunnen kleine breuken ontstaan die de wervelkolom instabiel maken. Er wordt gedacht dat instabiliteit van de wervelkolom kan leiden tot mechanische pijn: pijn die wordt verergerd als er kracht op de wervelkolom komt door bijvoorbeeld staan of lopen. Het zou kunnen dat pijn die wordt veroorzaakt door de tumor goed wordt aangepakt door bestraling, maar bestraling heeft geen effect op de mechanische pijn. Hoe instabieler de wervelkolom van patiënten, hoe minder kans ze hebben dat de bestraling effect zal hebben op hun pijnklachten. Ondersteuning voor deze hypothese werd gevonden in **hoofdstuk 4,** waar we een associatie zagen tussen spinale stabiliteit – uitgedrukt in een *Spinal Instability Neoplastic Score (SINS)* van 6 of lager – en een complete respons na bestraling. Er is geen associatie tussen de SINS en een gedeeltelijke respons na bestraling, wat betekent dat we de SINS nog niet kunnen gebruiken om response te voorspellen voor patiënten met wervelmetastasen.



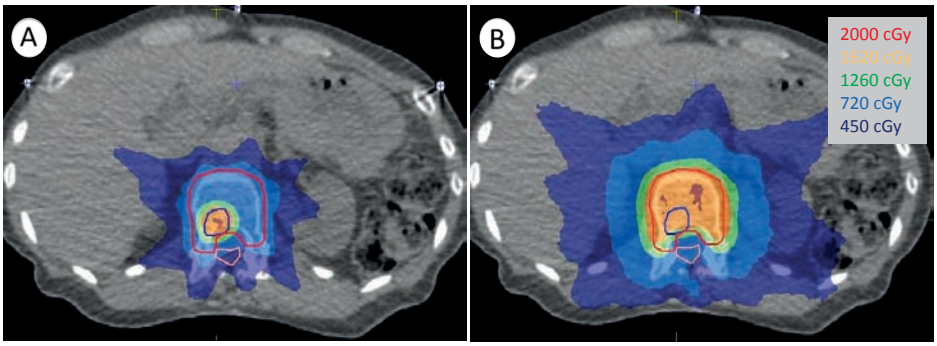
Figuur 2. *Receiver operating characteristic* curves die het onderscheidend vermogen weergeven van klinische variabelen (geslacht, primaire tumor en conditie, met de gestreepte lijn) en het onderscheidend vermogen als de SINS daaraan wordt toegevoegd (solide lijn) voor zowel gedeeltelijke (A) als complete (B) pijnresponse. De gestippelde lijn is de referentielijn, dat wil zeggen dat een test die op deze lijn uitkomt geen onderscheidend vermogen heeft.

Conventionele radiotherapie is dus de standaardbehandeling van botmetastasen, maar steeds vaker wordt gebruik gemaakt van hoge precisie bestraling (stereotactische bestraling). Stereotactische bestraling belooft een betere en langduriger pijnrespons, en het remmen van ziekteprogressie. Met stereotactische radiotherapie kan een tumor heel precies met een hoge dosis bestraald worden. In die gevallen is het cruciaal dat de tumor nauwkeurig en consequent wordt ingetekend. Om te weten te komen hoeveel variatie er is tussen verschillende waarnemers, hebben vijf radiotherapeuten (waarvan sommige in opleiding) 20 uitzaaiingen ingetekend met behulp van CT scans, CT scans in combinatie met MRI, en met alleen MRI scans (**hoofdstuk 5**). Intekeningen van de tumor waren significant groter op MRI scans (46 cm^3) in vergelijking met CT–MRI (40 cm^3) en CT (35 cm^3). Er zijn aanzienlijke verschillen tussen radiotherapeuten in interpretatie van wat precies de grenzen van de metastasen zijn, maar de grootste overeenkomst werd gevonden als alleen de MRI werd gebruikt.



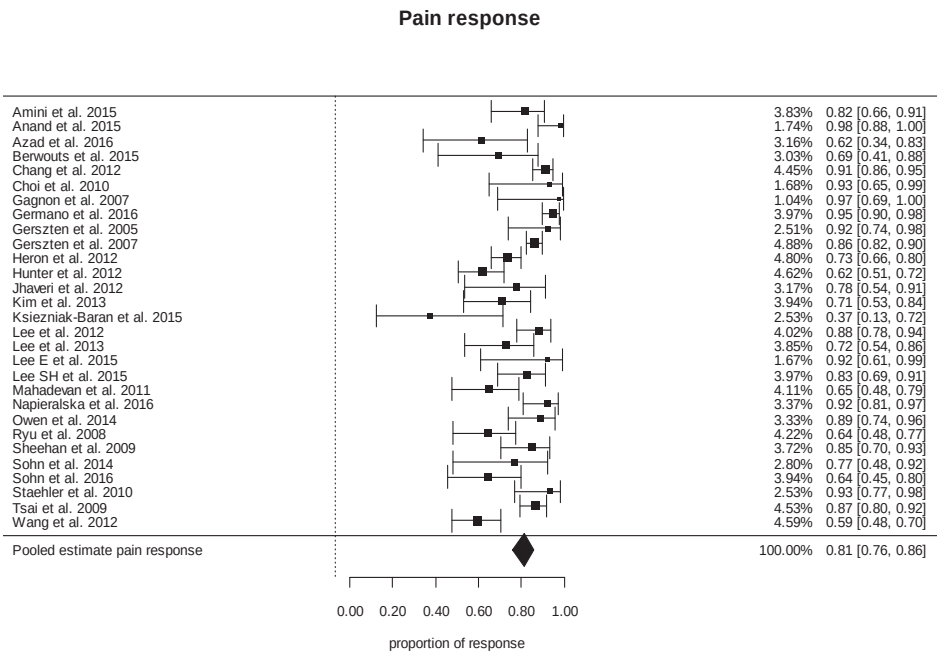
Figuur 3. Absolute volumeverschillen in cm^3 van intekeningen van de tumor, gebaseerd op CT–MRI en alleen MRI vergeleken met het gemiddelde volume van de laesie op CT (horizontale as). Patiënten zijn gerangschikt van kleinste gemiddelde volume op CT (patiënt 11: 1.2 cm^3) naar grootste volume op CT (patiënt 1: 184.7 cm^3).

Stereotactische bestraling heeft weinig bijwerkingen, maar er zijn zorgen over de vele inzakkingsfracturen die ontstaan na stereotactische radiotherapie (percentages tot 40% zijn gerapporteerd). Deze fracturen zijn moeilijk te voorkomen, omdat de tumor zich midden in het gezonde bot bevindt dat gespaard moet worden. In **hoofdstuk 6** stellen we voor om bestralingsplannen te maken waarbij de metastase een boost krijgt terwijl de dosis op het relatieve gezonde bot verlaagd wordt. Wanneer we plannen met deze benadering vergelijken met plannen waarbij de hele wervel met een hoge dosis bestraald wordt, zien we dat het omringende bot inderdaad veel beter gespaard wordt. Ook de organen die in de buurt van de wervelkolom liggen, bijvoorbeeld de grote vaten die voor de wervelkolom lopen, worden minder geraakt. Als bijkomend voordeel komt er zelfs een hogere dosis op de metastase zelf. Of deze verschillen ook zorgen voor klinisch relevante uitkomsten voor patiënten zal moeten blijken uit follow-up data van patiënten die met deze benadering zijn bestraald. Deze data moeten dan worden vergeleken met de data van patiënten die met een hoge dosis op de gehele wervel bestraald zijn.



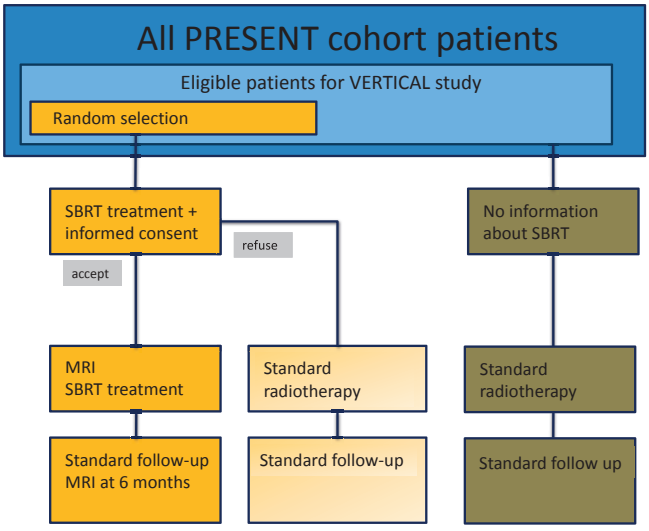
Figuur 4. De intekening en het bestralingsplan van een representatieve patiënt. (A) laat het bestralingsplan zien met de geïntegreerde boost op de tumor, terwijl de rest van de wervel wordt gespaard. (B) laat zien hoe het plan eruit was komen te zien als we geen boost zouden hebben gegeven. Voor deze patiënt konden we de dosis op het gezonde bot verlagen van 18 Gy naar 11 Gy.

Om een goede indruk te krijgen van hoe hoog de pijnresponse en lokale controle is na stereotactische radiotherapie, voerden we een systematische review en meta-analyse uit in **hoofdstuk 7.** Het gecombineerde resultaat van 29 artikelen waarin 1865 patiënten zijn geïncludeerd, laat zien dat de pijnrespons na stereotactische radiotherapie 81% is. Lokale controle na stereotactische radiotherapie is 86% – het gecombineerde resultaat van 3705 metastasen uit 40 studies. Het lijkt er dus op dat de pijnrespons na stereotactische radiotherapie hoger is dan na conventionele radiotherapie. Ook de lokale controle is hoog. Het is echter belangrijk om te weten dat de onderzoeksmethoden niet altijd even goed waren, bijvoorbeeld doordat niet altijd gecorrigeerd is voor het gebruik van pijnstillers. Van nog groter belang is dat de patiënten in deze studies voor het merendeel sterk geselecteerd waren. Zo zijn met name patiënten in een goede conditie onderzocht. Grote gerandomiseerde studies zijn nodig om stereotactische radiotherapie eerlijk te kunnen vergelijken met conventionele radiotherapie.



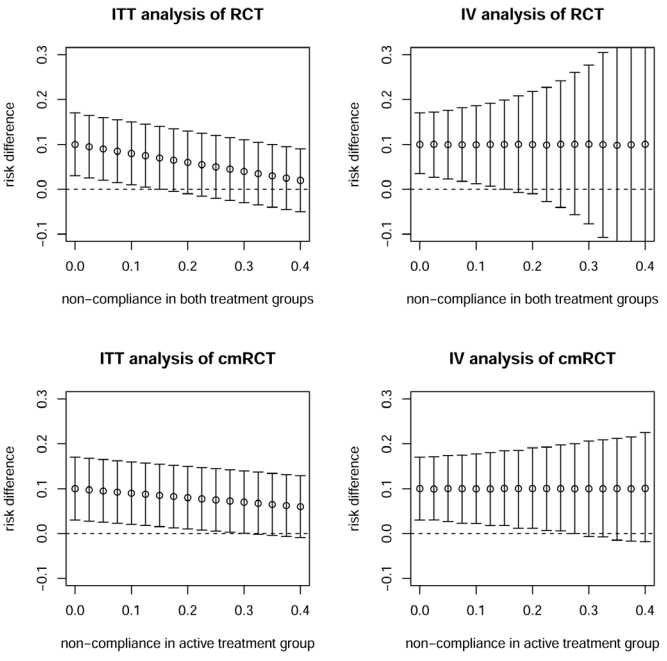
Figuur 5. Meta-analyse van de studies die bij patiënten met botmetastasen de pijnrespons na stereotactische radiotherapie evalueerden. De getallen tussen de vierkante haakjes zijn de 95% betrouwbaarheidsintervallen.

Ondanks dat dus nog niet bewezen is dat stereotactische radiotherapie beter is, worden er al wel veel patiënten behandeld met deze nieuwe techniek. In **hoofdstuk 8** wordt daarom de eerste gerandomiseerde studie binnen het PRESENT cohort gepresenteerd: de VERTICAL trial. In de VERTICAL trial wordt onderzocht of stereotactische radiotherapie beter is dan conventionele radiotherapie door gebruik te maken van het *cohort multiple randomized controlled trial* (cmRCT) design. De basis is het PRESENT cohort, waarvoor alle patiënten met botmetastasen die verwezen worden naar de afdeling radiotherapie of orthopedie worden gevraagd. Patiëntkenmerken worden genoteerd bij aanvang van deelname en op vaste tijdstippen worden uitkomstmaten gemeten. Ook kunnen patiënten toestemming geven om gevraagd te worden voor experimentele studies. Binnen PRESENT worden 110 geschikte patiënten geïdentificeerd (namelijk patiënten met niet eerder bestraalde, pijnlijke botmetastasen die in een redelijke conditie zijn). Aan een willekeurige selectie van 55 patiënten wordt de nieuwe behandeling met stereotactische bestraling aangeboden, die ze mogen accepteren of weigeren. De overige geschikte patiënten worden niet benaderd en worden behandeld met conventionele radiotherapie zodat ze als controlegroep kunnen dienen. Het cmRCT design kan een veelbelovend alternatief zijn voor de klassieke RCT omdat er minder teleurstellingsbias is bij de controlepatiënten, inclusiesnelheid hoger is, en resultaten beter te generaliseren kunnen zijn.



Figuur 6. Het design van de VERTICAL studie. Patiënten met botmetastasen worden gevraagd deel te nemen aan een groot observationeel cohort (donkerblauwe box). Patiënten in het PRESENT cohort die geschikt zijn voor stereotactische radiotherapie komen in een zogenaamd subcohort (lichtblauwe box). Willekeurig geselecteerde patiënten uit het subcohort wordt stereotactische radiotherapie aangeboden (oranje box). De uitkomsten van deze patiënten worden vergeleken met de uitkomsten van de overige patiënten die de standaardbehandeling hebben ondergaan (bruine boxen).

Gerandomiseerde onderzoeken (RCTs) zijn de gouden standaard om nieuwe behandelingen te onderzoeken, maar zijn moeilijk en duur om uit te voeren. Het cmRCT design biedt een raamwerk om meerdere behandelingen gelijktijdig gerandomiseerd te evalueren en is een veelbelovend alternatief voor de klassieke RCT. In **hoofdstuk 9** evalueren we de methodologische aspecten van het uitvoeren van een cmRCT. Vanwege de timing van de randomisatie, is de uitval in de groep die de nieuwe behandeling aangeboden kregen waarschijnlijk groter dan bij een klassieke RCT. Dit wordt (deels) gecompenseerd door de deelnemers in controlegroep, die niet weten dat er een andere behandeling is en in principe allemaal de standaardbehandeling ondergaan. Daardoor zullen ze minder snel overstappen naar de andere groep binnen de studie. Ook zullen ze waarschijnlijk eerlijker uitkomstmaten als pijnscores rapporteren, omdat ze niet beïnvloed worden door teleurstelling die ze kunnen ervaren als ze niet de nieuwe behandeling krijgen. De standaardbehandeling in een studie zal daarom ook meer lijken op de standaardbehandeling in de dagelijkse praktijk. We beargumenteren dus dat resultaten van een cmRCT even valide zijn als van een klassieke RCT. Of het ook een efficiënter design is, hangt af van hoeveel patiënten de nieuwe behandeling zullen weigeren.



Figuur 7. Getallenvoorbeeld van een intention to treat-analyse en instrumentele variabele-analyse in zowel een klassieke RCT en een cmRCT. Als in een klassieke RCT in beide groepen 10% van de patiënten weigert, weigeren dus in totaal 10% van alle studiepatiënten. In een cmRCT kunnen alleen patiënten in de experimentele arm weigeren, wat dan neerkomt op 5% van de totale studiepopulatie. Naar verwachting echter zullen er meer patiënten uitvallen in de experimentele arm. Hiervoor compenseert het cmRCT design met minder patiënten die zullen weigeren in de controlegroep.

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Joanne van der Velden was born on May 4th, 1988, in Vlaardingen, The Netherlands. After graduating from the Guido de Brès in 2006, she started medical school at the University of Utrecht. During her studies, she was active as a student researcher at the Julius Center for Health Sciences and Primary Care under supervision of prof. dr. J.J.M. van Delden. In 2013, she obtained her medical degree after which she started as a PhD candidate at the Department of Radiation Oncology of the University Medical Center Utrecht. Under supervision of prof. dr. H.M. Verkooijen, dr. J.J. Verlaan, and dr. Y.M. van der Linden, she coordinated the set up of the PRESENT cohort, the first cmRCT in palliative care in the outpatient oncology setting. She also initiated and coordinated the VERTICAL study, the first randomized trial within the PRESENT cohort. In 2015, she went abroad to perform a research internship at the Department of Radiation Oncology, Sunnybrook Health Science Center, Toronto, Cananda, under supervision of dr. E. Chow and dr. A. Sahgal. This year, she will complete her postgraduate master of Epidemiology. At first, she thought she wanted to be a radiologist, but she got inspired by the work of her colleagues from the radiotherapy department. Therefore, she is currently a radiation oncology resident under supervision of dr. J.L. Noteboom and drs. I.E. van Dam. She will proceed combining clinical work with research, as this is, as she believes, the best way to formulate clinically relevant and urgent research questions. Work is one of her great passions, but besides that, she loves reading, snowboarding, watching shows on Netflix, and her husband Mart Keuning.

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