Studies on the treatment of BONE METASTASES

Bart Jacob Pielkenrood

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Studies on the treatment of bone metastases

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(met een samenvatting in het Nederlands)

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Door

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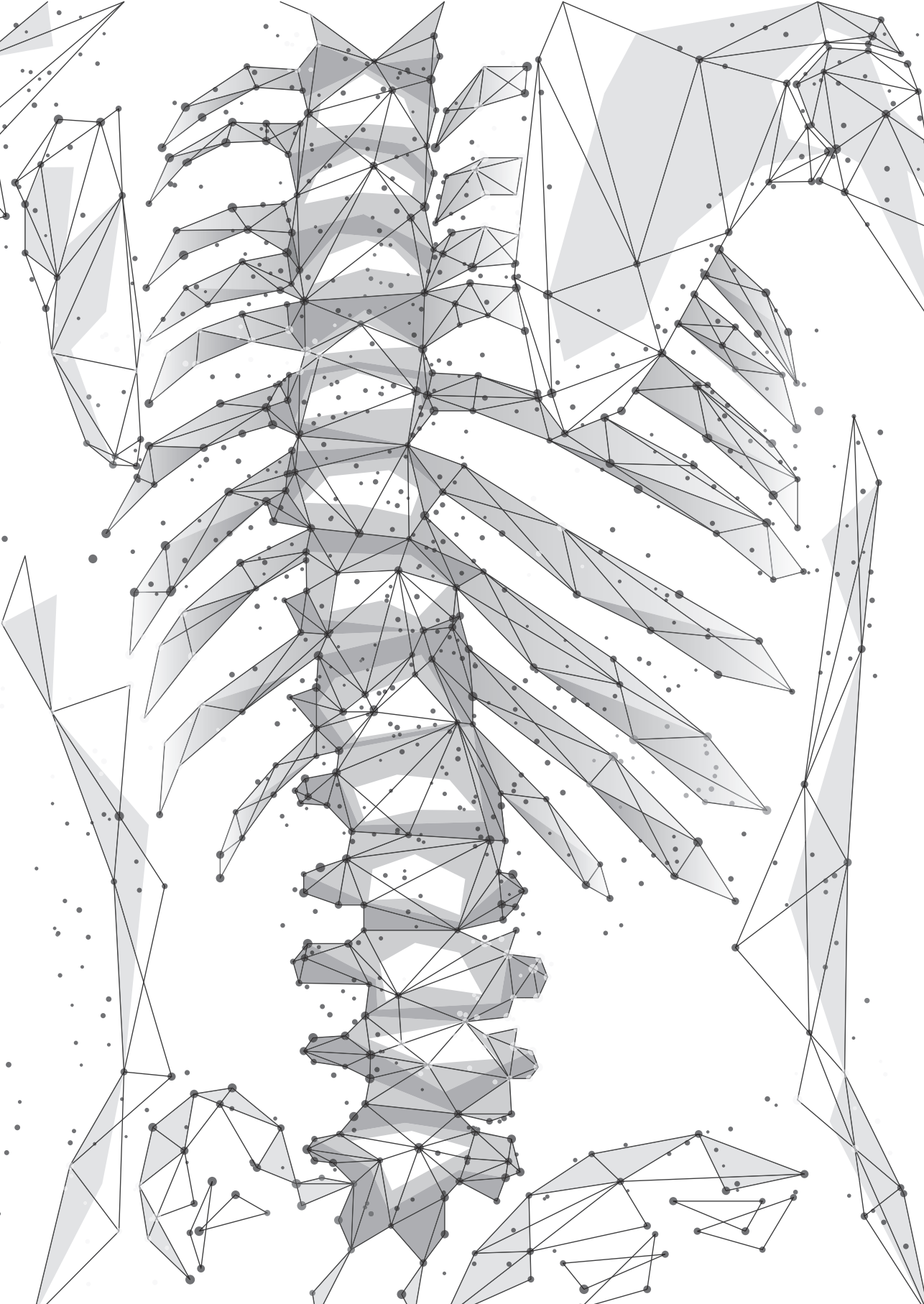

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CHAPTER 1

General introduction and thesis outline

Background

Bone metastases are increasingly common, incurable, cause pain, and have a large impact on the patient's quality of life (QoL).[1,2] Bone metastases are often a component of advanced cancer and are most commonly seen in patients with breast, prostate, lung, and kidney cancer. At post-mortem examination, bone metastases were found in 68% of the patients with prostate cancer and 73% of the patients with breast cancer.[3] In 2015, approximately 25.000 patient were diagnosed with spinal metastases in the Netherlands.[4] Approximately 70% of all bone metastases are located in the spinal column.[5]

When cancer spreads to the bone, it can interfere with the natural equilibrium of bone turnover, which is the finely balanced and coupled physiological process of bone resorption and bone formation.[6] Under the influence of cytokines among other things, excreted by a metastasis, this bone equilibrium could shift to an increased bone resorption with little bone formation.[7] These lesions are defined as lytic. The opposite can also happen: an increased bone formation and little bone resorption. These lesions are defined as blastic. Metastases can also be a lytic and blastic mixture. Metastases from prostate cancer are often blastic while metastases from kidney cancer are often lytic and from breast cancer are mixed. [7]

In approximately half of the patients, the metastases are found because of a skeletal related event. In the other half, metastases are detected during routine follow-up. One of the most common complications of bone metastases is (severe) bone pain, which is complex and multifactorial. Bone, including the periost, is highly innervated by sensory neurons.[8,9] It is thought that bone pain is, among others, caused by mechanical stress on these neurons due to tumor growth. Bone pain can also be caused by damage to the neurons due an acidic microenvironment caused by increased osteolytic activity.[9]

The altered equilibrium between osteoclasts and osteoblasts has a negative impact on the bony architecture and bone density.[7,10] And therefor, has an impact on the mechanical integrity of the spine, and may increase the risk of spinal instability, (progressive) deformity, and/or pathological fractures in patients.[7,10] Tumor growth, as well as deformity or pathological fractures, can cause spinal nerve root or spinal cord compression. These complications have a large impact on the patient's quality of life (QoL). The complications that are found in patients with bone metastases may have many expressions and therefore, the treatment requirements vary.[11]

While bone metastases cannot be cured, the impact of bone metastases on the overall survival can be reduced. When pain and/or the risk of pathological fractures

is reduced, the patient's well-being on a physical and functioning level as well as mental well-being will improve.[12,13] Mobility and functioning are known to have a great impact on the general condition and hence overall survival.[11]

Many patients with bone metastases are in a general poor condition due to the advanced cancer. Median survival of patients with a combination of bone and visceral or brain metastases is limited (approximately seven months), but is much longer in patients with bone metastases only.[1,14] A limited life expectancy impacts the treatment options and surgery is often not possible nor desirable in patients. Patients with limited systemic disease and severe pain or spinal instability, could benefit greatly from surgery.

The treatment of bone metastases

The treatment of bone metastases generally focusses on pain reduction and preserving or improving QoL. The initial step of the treatment of bone pain is the use of analgesics. This can be done according to the World Health Organisation's 'analgesic ladder' in which a physician can start with prescribing non-opioids such as paracetamol and non-steroid anti-inflammatory drugs such as naproxen. Often, the use of these drugs is insufficient in patient with bone metastases and strong opioids can be added.

Conventional radiotherapy (cRT) has a strong position in the treatment of painful bone metastases. Previous studies showed that a treatment with single fraction of 8 Gray (Gy) is as effective as multifraction treatments for pain relief.[1,15–17] Especially in patients with a limited life expectancy, single fraction cRT is time efficient as it can often be administered within several days, has limited side effects. The majority of the patients (60%) have a sufficient pain response after single fraction cRT, pain relief is often noticed within 4-6 weeks.[1] That still leaves about 40% of the patients who do not have an adequate pain response and must rely on analgesics for pain relief and surgery for unstable cases.
Over the past decades, radiotherapy techniques have been improved and new techniques have been developed. One of the most promising techniques is Stereotactic Body Radiation Therapy (SBRT).[18–20] Using SBRT, a higher and more focussed RT dose can be administered, which showed to be safe in patients with bone metastases.[18] And it is expected that this ablative dose could improve pain response. To compare pain response and change in QoL after cRT and SBRT, we performed the VERTICAL trial (comparing conVEntional RadioTherapy with stereotactIC radiotherapy in patients with spinAL metastases, chapters 4 and 5).
When gross spinal instability develops, spinal surgery may be necessary to prevent further deterioration of spinal deformity or development of neurological deficits.[21,22] If the spine is stable, surgery is often not necessary. Radiotherapy

could restore the balance of osteoclast and osteoblast activity, as the tumor no longer interferes with the bone turnover equilibrium.[6,23] The restored equilibrium is thought to promote bone growth and could therefore improve the bone architecture, which in turn improves the mechanical integrity of the spine. Surgery could no longer be necessary if the mechanical integrity could be restored sufficiently after radiotherapy.

Evaluation of the treatment

When new treatment modalities are developed, they should be evaluated and compared to the standard treatment. With well-designed comparison trials, the superiority of effect and/or side-effect of the novel treatment can be shown in comparison to the standard treatment. Typically, this comparison is done in randomized controlled trials (RCT). Classic RCTs come with downsides. Multiple trials on the treatment of bone metastases took longer than expected, were completed with less patients than planned or were terminated early due to lack of accrual.[24,25] The slow or lack of accrual could be linked to the general condition of the patient and the uncertain effects of the intervention treatment.

As alternative to the classic RCTs, the Trials within Cohorts (TwiCs) design was created.[26] In TwiCs, all patients with a similar disease and/or treatment are included in an observational prospective cohort, in which – amongst others- clinical characteristics, tumor control, survival, and patient reported outcomes are prospectively collected. This cohort forms a base to recruit patients for a randomized trial for a novel intervention. [26,27] In a regular RCT, patients are informed on both treatment arms before they are randomized.

Since 2013, all patients who are treated with radiotherapy for bone metastases are asked to participate in the PRospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort. In addition to their clinical data, patients fill out PRO questionnaires at 2, 4, 6, 8 and 12 weeks and every three months thereafter. The VERTICAL trial was executed following the TwiCs design, therefor the patients were selected from the PRESENT-cohort.

Patient selection for treatment

When a metastatic lesion causes (an increased risk of) spinal instability or pathological fractures in long bones, surgery may be necessary. Surgery for (spinal) bone metastases may relieve pain and decreasing the risk of complications and mortality and improve QoL.[28] Life expectancy of patients should at least exceed the recovery time of the surgery, which is generally defined as 12 weeks.[21,29]

Patients with bone metastases vary in general health condition, comorbidities and general prognosis. In addition, bone metastases' biologic behaviour varies between patients. While patient and their tumor biology are complex, the estimation of the life expectancy is a significant component of the choice of the treatment decision.

Multiple models have been constructed and later improved to estimate the patient's life expectancy. These models included multiple factors such as the primary tumor, patient's general condition and the presence of other metastases than the bone metastases. Unfortunately, these models showed to have limited accuracy with a maximum of 70% correct estimations of survival of patients with spinal metastases.[30]

In recent years, body composition came into focus in research on survival after cancer diagnosis.[31–35] The (change in) body composition, especially visceral fat area and total muscle area, were found to be associated with survival.[32,33,35]. Body composition can be measured on CT-scans, which are performed routinely in patients undergoing radiotherapy and/or surgery for spinal bone metastases. Measuring the fat and muscle areas on the level of the third lumbar vertebra correlates with the total fat and muscle area of the body.[35–37] The use of these factors could benefit the estimation of the prognosis in patients with bone metastases.

Purpose and outline of this thesis

To improve the treatment of patients with bone metastases, one must focus one multiple aspects of the treatment. The basis of improving the treatment is selection of the right patient for the right treatment. The treatment itself can be improved using novel treatment techniques, but the effect of these novel techniques must be evaluated properly. Furthermore, alternatives to invasive treatments should be considered.

In *chapter* 2, the impact of body morphology on life expectancy in patients with spinal metastases was analysed. Factors such as the subcutaneous and visceral fat area, total muscle area and muscle density could contribute to the prediction of a patient's prognosis.

As the life expectancy is especially important in the consideration for surgery, *chapter 3* focusses on the impact of the body morphology in patients undergoing surgery for spinal metastases. For this comparison, patients were included in the John Hopkins Medical Centre in Baltimore, Maryland, United States.

The results of the VERTICAL trial are discussed in *chapters 4 and 5. Chapter 4* focusses on the effect of SBRT vs. cRT on the pain scores and the feasibility of the

TwiCs design in patients in the palliative phase. *Chapter 5* focusses on the effect of cRT and SBRT on QoL. Lastly, in *chapter 6*, remineralization of spinal metastases after radiotherapy was evaluated as radiotherapy could be an alternative to surgery in a selected group of patients to prevent complications.

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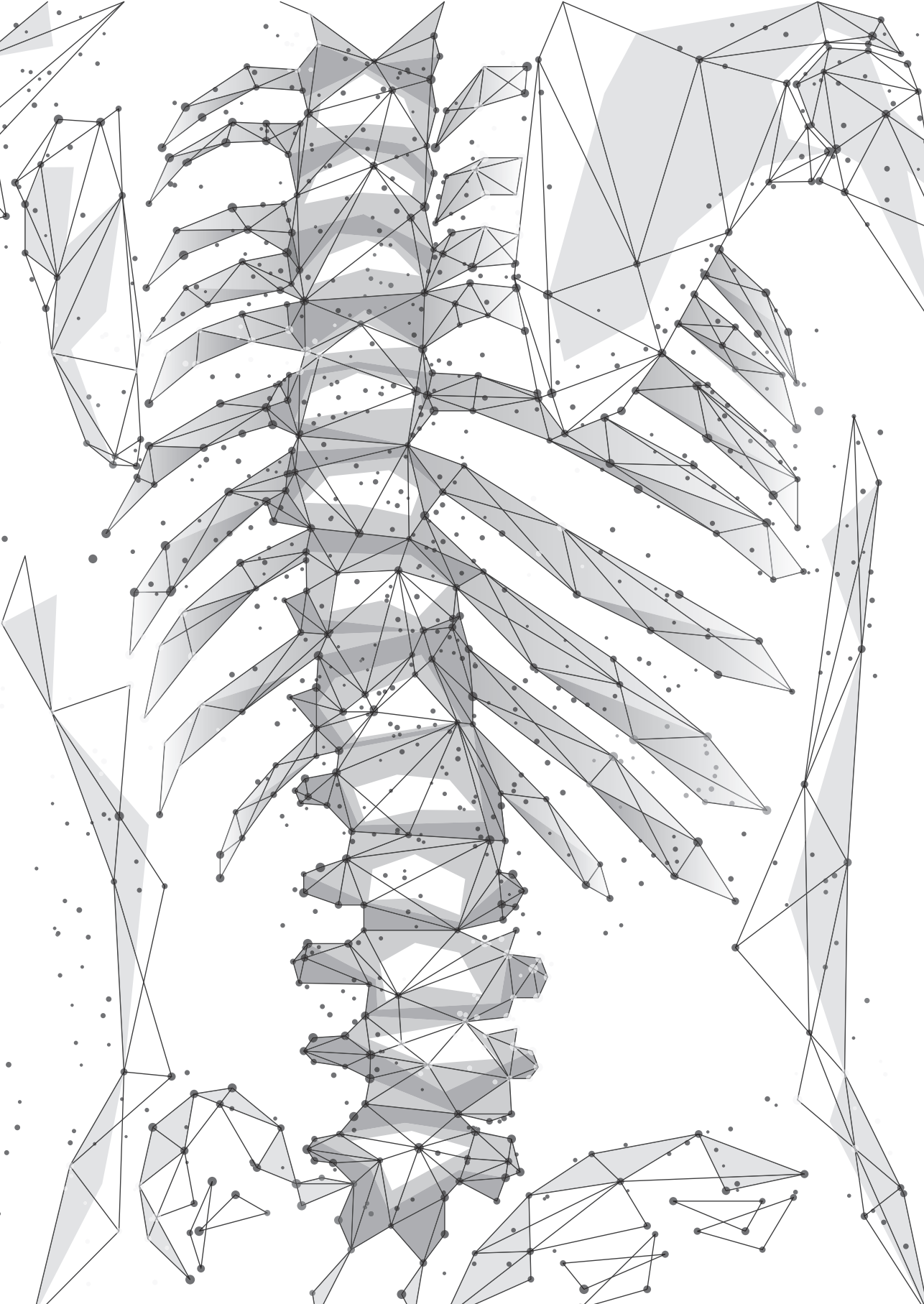

CHAPTER 2

Impact of body fat distribution and sarcopenia on the overall survival in patients with spinal metastases receiving radiotherapy treatment: A prospective cohort study

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Abstract

Introduction: An increasing number of patients is diagnosed with spinal metastases due to elevated cancer incidence and improved overall survival. Patients with symptomatic spinal bone metastases often receive radiotherapy with or without surgical stabilization. Patients with a life expectancy of less than 3 months are generally deemed unfit for surgery, therefore adequate pre-treatment assessment of life expectancy is necessary. The aim of this study was to assess new factors associated with overall survival for this category of patients.

Patients and methods: Patients who received radiotherapy for thoracic or lumbar spinal metastases from June 2013 to December 2016 were included in this study. The pre-treatment planning CT for radiotherapy treatment was used to assess the patient's visceral fat area, subcutaneous fat area, total muscle area and skeletal muscle density on a single transverse slice at the L3 level. The total muscle area was used to assess sarcopenia. Furthermore, data were collected on age, sex, primary tumour, Karnofsky performance score, medical history, number of bone metastases, non-bone metastases and neurological symptoms. Univariable and multivariable cox regressions were performed to determine the association between our variables of interest and the survival at 90 and 365 days

Results: A total of 310 patients was included. The median age was 67 years. Overall survival rates for 90 and 365 days were 71% and 36% respectively. For 90- and 365-day survival, the Karnofsky performance score, muscle density and primary tumour were independently significantly associated. The visceral or subcutaneous fat area and their ratio and sarcopenia were not independently associated with overall survival.

Conclusions: Of the body morphology, only muscle density was statistically significant associated with overall survival after 90 and 365 days in patients with spinal bone metastases. Body fat distribution was not significantly associated with overall survival

Introduction

The overall survival of cancer patients has increased, due to early detection and improved treatment. [1]Because of this increased survival, more patients develop metastases, with metastases in the skeleton being the predominant site.[2] Most bone metastases are located in the spinal column, where they can cause pain, deformity, fracture, spinal instability and neurological deficits.[3,4] In patients with symptomatic spinal metastases, radiation therapy with or without surgical stabilization is often necessary.[3] When the life expectancy of a patient is less than three months, the quality of life is generally considered to be hampered too much by the time needed for recovery and revalidation to justify the procedure. [5,6] Therefore, to determine the optimal treatment for individual patients, appropriate estimation of expected survival is necessary beforehand, as a patient might not benefit from a demanding intervention. [5–7]

At this moment, patient survival is estimated using clinical factors such as primary tumour biology, the presence of visceral/brain metastases and (preoperative) performance scores, but the prognostic value of these factors combined is moderate.[6,8] Evidence on other factors such as nutritional status as prognostic factors (e.g. biochemical markers, weight or BMI) is still limited.[9,10] In recent years, an increasing number of studies have focused on body composition as a new and promising parameter for predicting prognosis in patients with malignancies. [11–13] Body composition refers to the distribution of visceral and subcutaneous fat, obtained from information on axial CT-slices at the level of the third lumbar vertebra (L3) and also includes muscle area and muscle density.[13–15]

The aim of this study was to evaluate whether difference in body composition, including visceral fat area, subcutaneous fat area, total muscle mass using the skeletal muscle index and muscle density, were associated with survival in patients with spinal metastases.

Patients and Methods

Patients were selected from a prospective cohort which included all patients receiving radiotherapy for bone metastases at a single center since June 2013. All patients signed informed consent for the use of their clinical baseline and follow-up data, including self-reported quality of life and pain scores. The study protocol was approved by the Institutional Review and Ethics Board of our hospital. For this study, all patients who were treated with radiotherapy only for thoracic or lumbar spinal bone metastases between June 2013 and December 2016 were included. There was no distinction on radiotherapy scheme or modality as this did not influence patients' overall survival. In the same way, no distinction was made on

concurrent (systemic) therapy at inclusion. Patients' medical records were used to collect patient characteristics. Characteristics included the Karnofsky Performance Score(KPS) to estimate general condition and the Charlson Comorbidity Index(CCI) to take medical history into account.[16] For retrieving a patient's vital status, a governmental database was used.

CT-measurements

For all patients, routine radiotherapy treatment planning CT scans were performed, using a 16-detector row CT scanner (Brilliance, Philips Medical Systems, Eindhoven, The Netherlands). Images were reconstructed at a slice thickness of 3 mm. A single trained observer, blinded to the clinical information of the patients, performed all body morphology measurements. The reproducibility of these measurements has proved to be very high.[17] One transverse CT image of the inferior surface of the L3 vertebral body was selected to manually delineate the abdominal muscle wall with VolumeTool, an in-house developed delineation tool to help radiotherapy treatment planning.[18] Delineation of the abdominal muscle wall included the psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal oblique and rectus abdominus muscles. The subcutaneous fat area (SFA), visceral fat tissue area (VFA), total muscle area and muscle density were measured using tissue-specific absolute Hounsfield units (HU) thresholds.[19,20] To determine muscle density, the mean HU of the muscle area was measured. Decreased muscle density is an indicator for an increased lipid concentration in the skeletal muscle and is a known proxy for decreased muscle function.[12] For the measurements of skeletal muscle, HUs from -29 to +150 were used, for subcutaneous and intra-muscular fat the value used ranged from -190 to -30 and for visceral fat the value ranged from -150 to -50 (Figures 1 and 2).[2] Subsequently, the VFA/SFA ratio was calculated by the simple division of the values for VFA and SFA. The skeletal muscle index was calculated by dividing the total muscle area by the square of the patient's height in meters. The cut-off values for sarcopenia were $<52.4\ cm^2/m^2$ for males and $<38.5\ cm^2/m^2$ for females.[14,21]

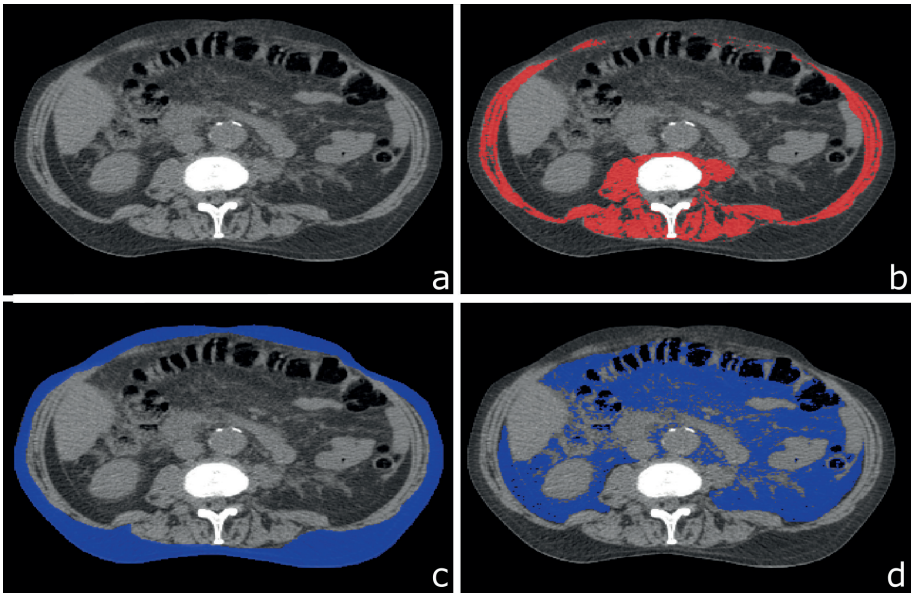

Figure 1. Example of a CT-analysis. (a) base CT-scan (b) total muscle area measurement (c) subcutaneous fat area measurement (d) visceral fat area measurement.

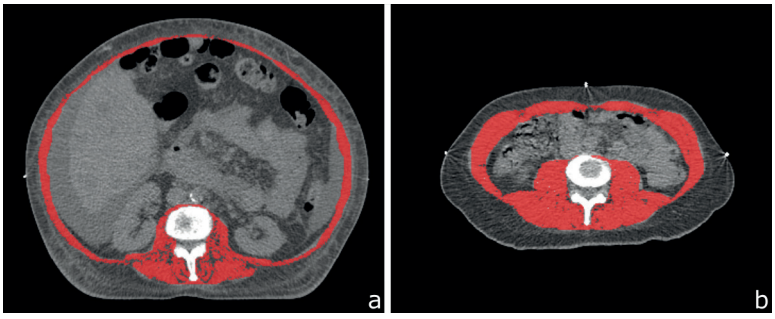

Figure 2. Example of muscle density. (a) patient with low muscle density. (b) patient with high muscle density.

Statistical Analysis

Continuous data was presented as mean with standard deviation (SD) for normally distributed continuous variables and median with interquartile range (IQR) for not normally distributed and imputed continuous variables. Normality was tested using the Shapiro-Wilk test. Categorical data are presented as counts with percentages.

Survival was defined as days between start of radiation therapy and date of death from all causes, or end of follow-up on 31st of March 2018. There was no loss to follow up due to the use of the up to date governmental database. As some data were included retrospectively, missing data were analysed for patterns of randomness, imputation was done with multiple imputation using the Markov Chain Monte Carlo method. Results of the imputation were checked using convergence plots. The KPS was analysed as a score from 1–10. Using imputed data, univariable Cox regression analysis was performed to compute mortality hazard ratios with 95% confidence interval (95% CI). A multivariable Cox regression was performed to adjust for factors associated with outcome in univariable analysis for survival after 90 and 365 days **.** Patients were censored after 90 and 365 days for the corresponding analysis. When using categorical variables, the largest group within that variable was used as reference group. Before multivariable analysis, collinearity was tested using the Variance Inflation Factor(VIF) as well as proportionality assumptions for the Cox regression analysis. [22,23] Variables were excluded if the VIF was >10 and reconsidered with VIF>5. [22] Statistical analyses were performed using SPSS, IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.[20]

Results

Study Population

A total of 310 patients with spinal metastases treated with palliative radiation therapy was included. Median follow-up was 202 days (IQR 73-576) and overall survival rates after 90 and 365 days were 71% and 36% respectively. The majority of patients was male (63%) (Table 1). The most common primary tumour originated from the lung (28%), followed by prostate and breast (27% and 18% respectively). Non-osseous metastases were present in 152 patients (49%), 22% of all patients had liver metastases and 3% had brain metastases. In 9% of the patients, neurological symptoms as a result of epidural compression of the spinal cord/ cauda equina/nerve roots were present. Of these patients, 18 (6%) had ASIA-scale grade D, 7 (2%), 2 (0.6%), 1(0.3%) had ASIA scale C, B and A respectively.[24]

There was no collinearity between any variables, as all VIFs were <5. Partial residuals using the Schoenfeld residuals method showed a linear relationship between residuals and continuous data. Missing data was found in 180 patients (58%), the majority of missing cases was found in the Karnofsky performance score (n=134, 43%) and/or the patient's height (n=93, n=30%) which is necessary to determine sarcopenia. Comparison between patients with and without at least one missing value can be found in supplementary table 1. Supplementary figures 1 and 2 show the convergence plots of the imputation of the KPS and height.

Table 1. Imputed and original baseline characteristics of all patients with thoracic or lumbar bone metastases

	Original data	Imputed data
Sex (n, %)		
Male	194 (63)	194 (63)
Female	116 (37)	116 (37)
Age (median, IQR)	67 (60-75)	67 (60-75)
Karnofsky performance score (mean, SD)	70 (15)	70 (14)
Missing (n, %)	134 (43)	0 (0)
Charlson Comorbidity Index (median, IQR)	6 (6-7)	6 (6-7)
Visceral fat area (median, IQR)	139 (82-208)	139 (82-208)
Subcutaneous fat area (median, IQR)	159 (110-228)	159 (110-228)
VFA/SFA-ratio (median, IQR)	0.84 (0.51-1.27)	0.84 (0.51-1.27)
Skeletal muscle density (mean, SD)	25.1 (7.4)	25.1 (7.4)
Skeletal muscle index (mean, SD)	46.8 (9.3)	46.7 (9.1)
Sarcopenia (n, %)	80 (26)	119 (38)
Missing (n, %)	93 (30)	0 (0)
Primary tumor (n,%)		
Lung	86 (28)	86 (28)
Prostate	83 (27)	83 (27)
Breast	55 (18)	55 (18)
Other	86 (28)	86 (28)
Multiple bone metastases (n,%)	189 (61)	189 (61)
Non bone metastases (n, %)	152 (49)	152 (49)
Liver	70 (23)	70 (23)
Brain	9 (3)	9 (3)
Neurological symptoms (n,%)	28 (9)	28 (9)

Table 1. Imputed and original baseline characteristics of all patients with thoracic or lumbar bone metastases

Univariable analysis showed that an increased age, increased VFA/SFA-ratio, increased SFA or a decrease in muscle density and a diagnosis of sarcopenia increased the probability of death. A higher KPS and having breast or prostate cancer as primary tumour compared with cancer of the lung decreased the probability of death (Table 2).

In a multivariable analysis for survival at 90 days, decreased muscle density was associated with a decreased survival at 90 and 365 days, adjusted for clinical factors such as KPS and primary tumour type; HR 0.62 (95% CI 0.41-0.94) and 0.70 (95% CI 0.53-0.92), respectively (Table 3). The subcutaneous fat area and fat ratio, as well as the presence of sarcopenia, were not independently associated with overall survival at any time point.

Table 2. Univariable Cox proportional hazard analysis for the risk of death after radiotherapy for bone metastases using pooled imputed data

	90 days		365 days	
	Died within 90 days n (%)	**HR (95% CI)**	**Died within 365 days n (%)**	**HR (95% CI)**
Sex				
Male	64 (33)	ref	147 (71)	ref
Female	28 (24)	0.68 (0.44-1.07)	73 (53)	0.62 **(0.46-0.84)**
Age		1.02 **(1.00-1.04)**		1.02 **(1.01-1.03)**
Karnofsky Performance Scale per 10 points		0.67 **(0.56-0.81)**		0.76 **(0.68-0.86)**
Charlson Comorbidity Index		1.20 (**1.00-1.43)**		1.18 **(1.05-1.32)**
Visceral fat area per 100 cm^2		1.00 (0.80-1.25)		0.90 (0.77-1.06)
Subcutaneous fat area per 100 cm^2		0.79 **(0.63-0.99)**		0.69 **(0.59-0.81)**
VFA/SFA-Ratio†		1.40 **(1.03-1.90)**		1.36 **(1.11-1.67)**
Skeletal muscle index		0.98 (0.95-1.00)		0.99 (0.97-1.00)
Skeletal muscle density		0.93 **(0.90-0.96)**		0.95 **(0.93-0.98)**
Sarcopenia				
No	44 (23)	Ref	112 (59)	Ref
yes	48(40)	2.03 **(1.57-2.48)**	86 (72)	1.61 **(1.31-1.91)**
Primary tumor				
Lung	39 (45)	Ref	80 (90)	Ref
Breast	6 (11)	0.19 **(0.08-0.44)**	21 (38)	0.12 **(0.06-0.21)**
Prostate	16 (19)	0.33 **(0.19-0.60)**	47 (48)	0.30 **(0.20-0.44)**
Other	31 (36)	0.70 (0.44-1.13)	72 (80)	0.71 **(0.51-0.98)**
Multiple bone metastases				
No	30 (25)	ref	80 (66)	1.31 (0.98-1.75)
Yes	62 (33)	1.41 (0.91-2.17)	140 (74)	
Non-bone metastases				
No	41 (26)	ref	102 (64)	ref
Yes	51 (34)	1.38 (0.92-2.08)	118 (77)	1.57 **(1.18-2.07)**
Liver metastases				
No	62 (28)	ref	153 (71)	ref
yes	24 (34)	1.31 (0.83-2.09)	54 (77)	1.37 (1.00-1.88)
Brain metastases				
No	81 (29)	ref	199 (73)	ref
yes	5 (56)	2.19 (0.89-5.39)	8 (89)	1.86 (0.92-3.78)
Neurological symptoms present				
No	81 (29)	ref	198 (69)	0.73 (0.46-1.15)
yes	11 (39)	1.40 (0.75-2.64)	22 (79)	

Hazard ratios with 95% confidence interval in bold are statistically significant.
†VFA: visceral fat area, SFA: subcutaneous fat area

Table 3. Multivariable Cox proportional hazard analysis for the risk of death after radiotherapy for bone metastases using pooled imputed data.

	90 days	365 days
	HR (95% CI)	**HR (95% CI)**
Age	1.02 (0.99-1.04)	1.01 (1.00-1.03)
Karnofsky Performance Scale per 10 points	0.71 **(0.55-0.92)**	0.82 **(0.71-0.95)**
Charlson Comorbidity index	0.96 (0.77-1.18)	0.95 (0.83-1.09)
Visceral fat area per 100 cm^2	0.95 (0.58-1.56)	1.00 (0.72-1.40)
Subcutaneous fat area per 100 cm^2	1.04 (0.69-1.56)	0.83 (0.63-1.11)
VFA/SFA Ratio†	1.25 (0.65-2.41)	1.05 (0.67-1.66)
Sarcopenia		
No	Ref	Ref
Yes	1.48 (0.87-2.52)	1.34 (0.94-1.92)
Skeletal muscle density per 10 HU	0.62 **(0.41-0.94)**	0.70 **(0.53-0.92)**
Primary tumor		
Lung	Ref	Ref
Breast	0.22 **(0.09-0.54)**	0.19 **(0.11-0.32)**
Prostate	0.27 **(0.14-0.52)**	0.26 **(0.17-0.40)**
Other	0.83 (0.50-1.38)	0.77 (0.55-1.10)
Multiple bone metastases		
No	Ref	Ref
Yes	1.08 (0.67-1.75)	1.12 (0.82-1.53)
Non-bone metastases		
No	Ref	Ref
Yes	1.11 (0.69-1.81)	1.08 (0.78-1.48)
Neurological symptoms present		
No	Ref	Ref
yes	1.07 (0.54-2.13)	0.99 (0.61-1.62)

Hazard ratios with 95% confidence interval in bold are statistically significant.
†VFA: visceral fat area, SFA: subcutaneous fat area,

Discussion

This study aimed at investigating the association between body composition and overall survival in patients with spinal metastases treated with radiation therapy. To our knowledge this is the first study addressing the impact of body composition in patients who receive palliative radiotherapy for spinal metastases. In this study, we found that muscle density was significantly associated with overall survival at 3 months and 1 year, adjusted for Karnofsky performance score (KPS), Charlson comorbidity index (CCI) and primary tumour. We did not find an independent significant association between subcutaneous fat area (SFA), visceral fat area (VFA) or fat ratio (VFA/SFA) and survival of patients with spinal metastases receiving radiotherapy.

In previous studies, the effect of SFA, VFA, TMA, muscle density and the VFA/SFA-ratio have been assessed for overall survival and progression-free survival. In some studies, an increased VFA, SFA and VFA/SFA-ratio was associated with improved survival.[25] The general hypothesis proposed so far has been that patients with a high VFA and SFA are in a generally better condition because low volume of adipose tissue in patients is linked to cancer progression. However, other authors have reached opposite conclusions with their study results, arguing that worse survival in patients with increased VFA could be linked to the detrimental hormonal activity of adipose tissue.[9,11,18] The adipose tissue is known to produce vascular endothelial growth factor (VEGF), which is a recognized factor in tumour growth and tumoral angiogenesis.[11]

Patients with advanced cancer can suffer from cachexia, which is a systemic tissue-wasting process in which the patient loses fat, muscle tissue and muscle quality in the form of lower muscle density.[2,26–29] Cachexia could have a negative impact on overall survival, as the patient's general condition decreases.[26,29] Sarcopenia, which could be part of cachexia, but is also a syndrome in itself, is generally used as the term for loss of muscle mass and function. Unfortunately, there is limited consensus on the cut-off value for sarcopenia.[21,30] In our study, we used the cut-off value described by Prado et al. which is widely used.[21] In accordance with our results, Okumura et al. reported that a decrease in muscle density was associated with decreased overall survival of patients after resection of pancreatic cancer in 301 patients, and Nattenmüller et al. reported the same correlation in 200 patients with lung cancer having received chemotherapy. Furthermore, the association between a decrease in muscle density and decreased survival was also reported for multiple other primary tumours.[21,31,32] Similarly, in the study of Chambard and coworkers sarcopenia was also associated with worse outcome for patients with lung cancer and synchronal bone metastases.[29] However, sarcopenia was not independently associated with overall survival in primary, operable gastrointestinal cancers.[33] The present study is the first study concerning patients with spinal metastases and did not focus on, or select one specific primary tumour.[1] The study of Chambard et al. only took into account patients with synchronous bone metastases from lung carcinoma. Decreased muscle strength is a sign of poor prognosis and could be caused by low muscle density. In the present work we found an association between low muscle density and poor prognosis which was independent of other clinical factors as found in different studies as well.[2,34] Shachar et. al. performed a meta-analysis to look at the prognostic value of sarcopenia on overall survival in patients with solid tumours.[21] Contrary to our results, they found a significant difference in patients with and without sarcopenia in the multivariable analysis. In this study, we did find a significant difference in the univariable analysis, but not in the multivariable analysis. This could be due to the general condition of the cohort, as these are all patients with advanced metastatic cancer receiving palliative care.

During treatment and/or progression of disease in patients with advanced cancer, their body composition might change as patients lose weight due to loss of fat or muscle tissue. This change in body composition was described in the review by Pamoukdjian et al., where it was found that 39% of cancer patients had pre-treatment sarcopenia.[35] Neuromuscular impairment and its effects on mobility and function can also have a profound effect on muscle mass and strength.[36] Neuromuscular impairment was present in 9% of our patients, which could have confounded the association of muscle density and survival, but multivariable analysis showed the association to be independent of neuromuscular impairment.

In this and other studies, a single pre-treatment scan was used to assess body morphology instead of scans at multiple points in time. Nattenmüller and co-workers and Tan and co-workers assessed the change in body composition over a period of time, both with a mean follow-up of 4.4 months.[27] Nattenmüller et al. showed that decreasing weight and loss of muscle tissue after chemotherapy was associated with worse survival in 200 patients with lung cancer. This effect was not reported by Tan et al., which might be due to their limited number of patients (n=44).[27] For future research, follow-up scans to assess change in body morphology over time can be considered, to analyze if changes in body morphology are associated with overall survival in patients with spinal metastases. The revised Katagiri scoring system added laboratory outcomes to their original model, which includes C-reactive protein (CRP); lactate dehydrogenase (LDH); serum albumin; serum calcium corrected for albumin level; platelet count; and total bilirubin. [37] In their prognostic model, they found abnormal or critical laboratory values (e.g., CRP 0.4 mg/dL, LDH 250 IU/L, or serum albumin <3.7 g/dL or platelet count <100,000/lL, serum calcium level 10.3 mg/dL, or total bilirubin 1.4) were associated with decreased survival. Kardhade et al. also included multiple laboratory data in their machine learning model.[38] Nonetheless, the evidence of these models is still limited as there has not been an external validation yet. In addition, these laboratory values are limited or not available in patients who receive radiotherapy alone. In future modelling, the laboratory values might prove to be useful.

One of the limitations of this study is the missing data on KPS and patient height. Using multiple imputations, the missing data were imputed and pooled data were used for the single and multiple variable analyses, so all patients could be handled as complete cases. KPS still showed to be significantly associated with overall survival, independent of other factors. Next, the cohort used is heterogenous, which makes it hard to create a model on the factors associated with overall survival in this patient group. But this is also a strong point of this study, as it does make the model more pragmatic. Lastly, only patients treated with radiotherapy were included. It could be useful in further studies to also include surgically treated patients.

Conclusion

Better prediction of survival in patients with spinal metastases is crucial to optimize their care. CT analysis is an easy-to-perform measurement, as recent chest/abdominal CT-scans are available for most cases and for all patients who receive radiotherapy.[19] As previously found in other studies, Karnofsky performance score and primary tumour were independently associated with overall survival in patients with spinal metastases treated with palliative radiotherapy. In addition, we found that muscle density was independently associated with overall survival. A diagnosis of sarcopenia was associated with overall survival in the univariable analysis, but the association was not independently statistically significant. Pre-treatment (planning) CT-scan analysis may provide useful information which can contribute to better care. We conclude that an analysis of body fat distribution and sarcopenia can improve predictions of overall survival, and suggest that these measurements are of value for future clinical multifactorial prediction models for this category of patients.

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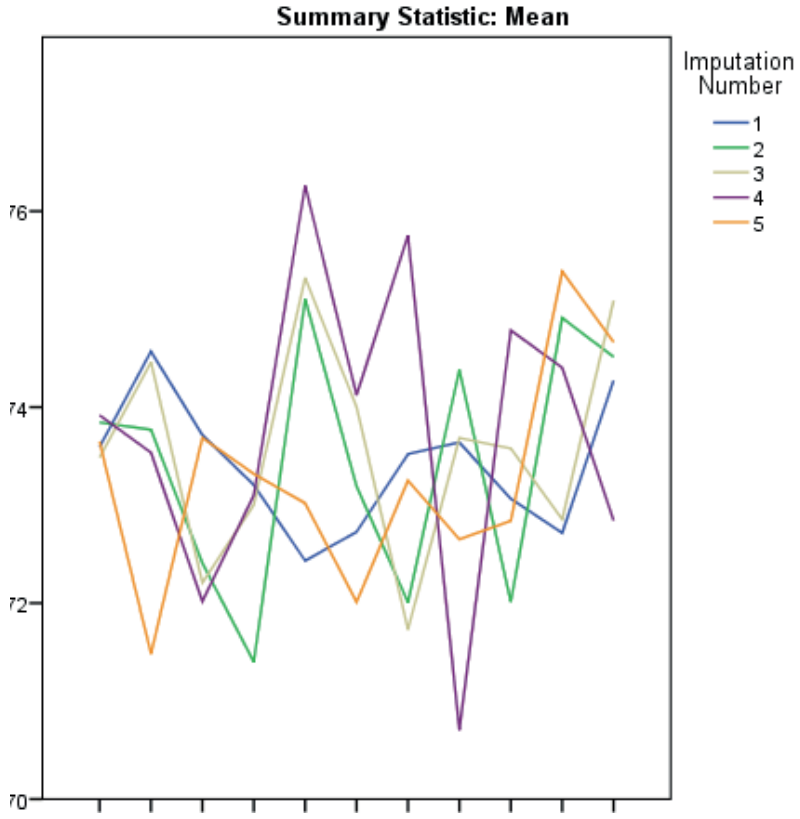
Supplementary data

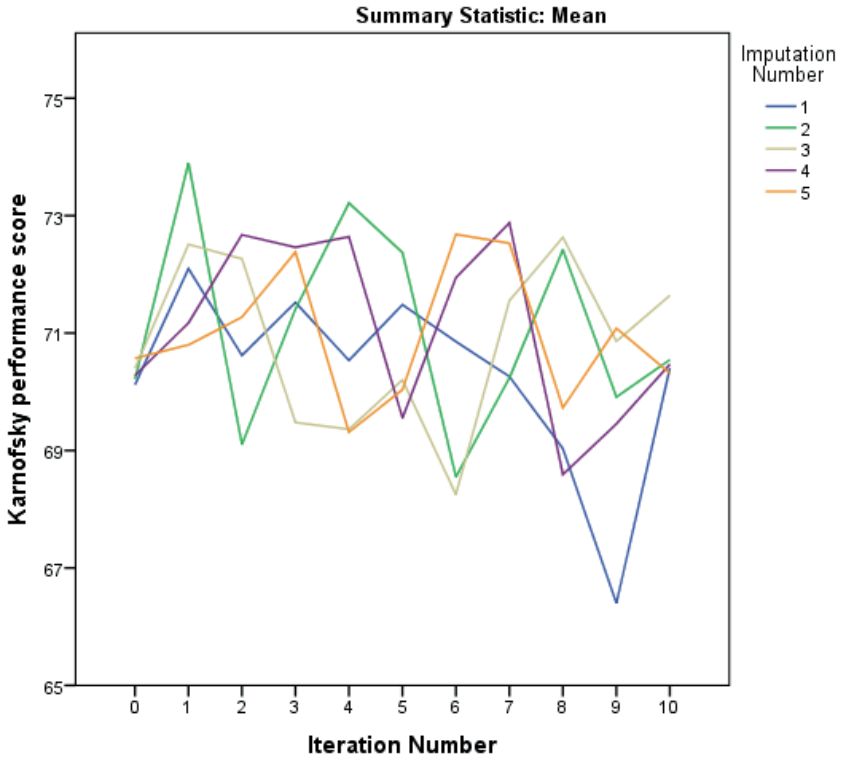
Supplementary table 1. Differences between patients without any or with at least one missing value.

	No missing values	≥1 missing value
Sex (n, %)		
Male	82 (63)	112 (62)
Female	48 (37)	68 (38)
Age (median, IQR)	66 (60-73)	69 (67-75)
KPS (median, IQR)	70, (60-80)	70 (60-71)
VFA (median, IQR)	133 (85-213)	16 (78-205)
SFA (median, IQR)	157 (108-250)	160 (110-215)
VFA/SFA-ratio (median, IQR)	0.87 (0.53-1.16)	0.83 (0.49-1.36)
SMI (mean, SD)	51 (9.8)	51 (8.5)
MA (mean, SD)	29 (6.5)	29 (6.5)
Sarcopenia (n, %)	68 (52)	44 (24)
Primary tumor (n, %)		
Lung	33 (25)	53 (29)
Prostate	22 (17)	33 (18)
Breast	34 (26)	49 (27)
Other	41 (32)	45 (25)
Multiple bone metastases (n, %)	75 (58)	114 (63)
Non bone metastases (n, %)	66 (51)	86 (48)
Liver	33 (25)	37 (21)
Brain	5 (4)	4 (2)
Neurological symptoms (n, %)	10 (8)	18 (10)

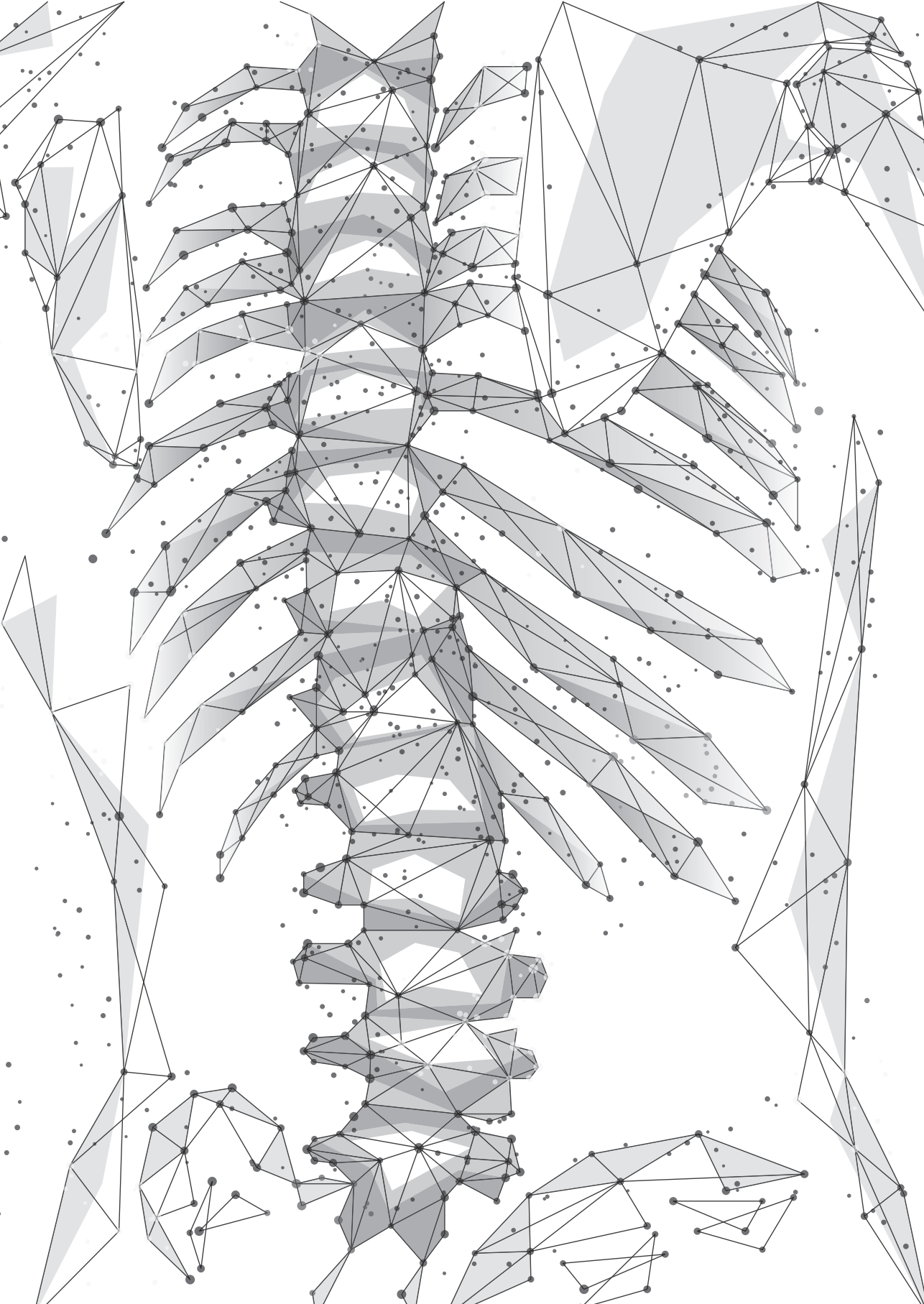
Abbreviations: IQR: interquartile range, KPS: Karnofsky Performance Scale, VFA: visceral fat area, SFA: subcutaneous fat area, SMI: skeletal muscle index, SMD: skeletal muscle density



Supplementary figure 1. Convergence plot of imputation of missing data in patient's height



Supplementary figure 2. Convergence plot of imputation of missing data in the Karnofsky Performance score



CHAPTER 3

Visceral Fat Volume from Standard Preoperative CT is an Independent Predictor of Short-Term Survival in Patients Undergoing Surgery for Metastatic Spine Disease

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Abstract

Objective: Determine the relationship of body morphometry to postoperative survival in patients with vertebral metastases.

Summary of Background Data: Most operations for vertebral metastases aim for palliation not cure, yet expected patient survival heavily influences treatment plans. We seek to demonstrate that preoperative fat and muscle volumes on standard-of-care computed tomography (CT) are independent predictors of survival after surgery for vertebral metastases. Materials and Methods: Included data were preoperative neurological status, adjuvant treatments, CT-assessed body composition, health comorbidities, details of oncologic disease, and Tomita and Tokuhashi scores. Body composition—visceral fat area, subcutaneous fat area, and total muscle area—were assessed on preoperative L3/4 CT slice with Image J software. Multivariable logistic regressions were used to determine independent predictors of 3-, 6-, and 12-month survival.

Results: We included 75 patients (median age, 57, 57.3% male, 66.7% white) with the most common primary lesions being lung (17.3%), prostate (14.7%), colorectal (12.0%), breast (10.7%), and kidney (9.3%). The only independent predictor of 3-month survival was visceral fat area [95% confidence interval (CI): 1.02–1.23 per 1000 mm2; P = 0.02]. Independent predictors of survival at 6 months were body mass index (95% CI: 1.04–1.35 per kg/m2; P = 0.009), Karnofsky performance status (95% CI: 1.00–1.15; P < 0.05), modified Charlson Comorbidity Index (95% CI: 1.11–7.91; P = 0.03), and postoperative chemotherapy use (95% CI: 1.13–4.71; P = 0.02).

Conclusions: Visceral fat mass was an independent, positive predictor of short-term postoperative survival in patients treated for vertebral metastases. As a result, we believe that the prognostic accuracy of current predictors may be improved by the addition of visceral fat volume as a risk factor

Introduction

Annually, >700,000 Americans are diagnosed with vertebral metastases, of which >18,000 will show signs of spinal cord compression or pathological spinal column instability.[1–6]

For most of these patients, the goal of surgery is palliation.[7,8] As a result, the decision to pursue operative management hinges heavily upon the expectation that patients will survive long enough to recover from and derive meaningful benefit from surgical intervention. Current evidence suggests a threshold of 3-6 months, with only patients having life expectancies exceeding this period being considered surgical candidates.[9,10]

Previous studies identify multiple factors influencing postoperative survival, including patient age, primary pathology, and extent of systemic disease. Recently though, research on patient survival following initial cancer diagnosis has identified body morphometry/composition to be independently associated with patient survival.[11–19] These studies have identified changes in visceral fat volume and total muscle volume as significant survival predictors.[11,14,17,19–23] Similar studies focusing on patients with spinal metastases have not yet been performed. The purpose of this study was to determine whether body morphometry parameters assessed on standard computed tomography (CT) imaging were significantly associated with overall survival in patients treated surgically for spinal metastases.

Material and methods

Study Design and Subjects

To collect patients for this study, we queried a retrospective database of all patients operated for spinal metastases at a single institution between January 2003 and December 2013 (IRB number: NA_00067508). Patients were eligible for included only if: (1) they were being treated for spinal instability or neurological deficit secondary to spinal metastasis; (2) they were above 18 years old; (3) they had records including postoperative survival, staging at time of surgery, and medical comorbidities; and (4) they had a pre-operative CT of their abdomen performed within 3 months of surgery. Patients not meeting these criteria were excluded.

Study Variables

The primary outcome was overall post-operative survival. Variables considered as predictors of patient survival included demographic variables [age, race, sex, body mass index (BMI)], oncologic history variables (primary tumor pathology, time between diagnosis of primary and spinal metastasis, pre-operative and postoperative

chemotherapy, surgical resection of primary) oncologic status variables (target lesion level, polyostotic vertebral involvement, visceral metastases, and extraspinal osseous metastases), pre-operative Frankel grade, Karnofsky performance status (KPS), ambulatory status, and Tomita and Tokuhashi scores. Also collected were radiographic measures of total muscle volume, visceral fat volume, and subcutaneous fat volume, and a modified Charlson Comorbidity Index (CCI), which was calculated by excluding the primary tumor and age components of the standard CCI.

Measurement of Body Morphometry Variables

Total muscle area (TMA), visceral fat area (VFA), and subcutaneous fat area (SFA) were measured using the L3/4 axial slice of standard abdominal CT scans as reported by Guiu et al.[13] This has been used repeatedly in the literature and VFA, SFA, and TMA as measured on this single slice have been highly correlated with total volume measures for these tissue categories.[24] The L3/4 space was identified by scanning caudocranially from the L5/S1 disk space until the first image showing the L3/4 disk space was identified. This image was uploaded into the Trainable WEKA Segmentation plugin for ImageJ software (NIH, Bethesda, MD).[25] Using this freely available plugin, fat, muscle, intestine, disc space, bone, and air were identified to provide references for the different tissue types that we desired to distinguish during image analysis. The segmentation feature of the plugin then divided the image into these various tissue types based upon pixel intensity and nearest neighbor assumption (Fig. 1). Entrainment was performed individually for each image to ensure results were not affected by variation in individual image quality or postimaging modifications performed by the radiology department. The VFA, SFA, and TMA were then calculated using the integrative function of ImageJ.

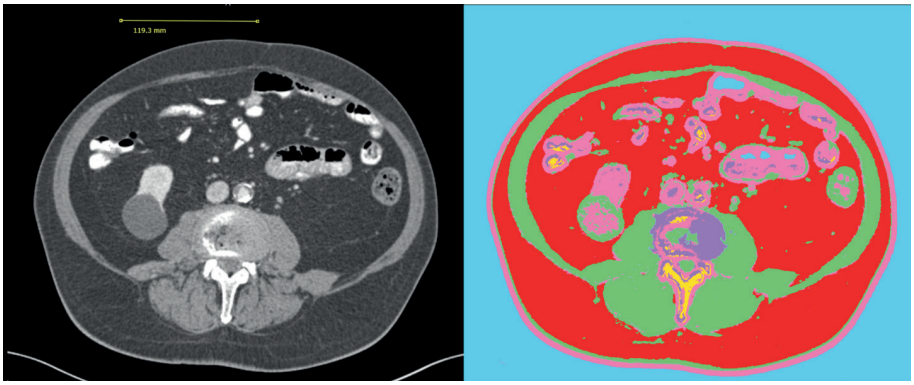

Figure 1. Example of processed image output from WEKA Segmentation Application. A, Example of raw L3/4 cross-section with reference bar. B, Example of processed image output from WEKA Segmentation plugin showing partition of computed tomography into distinct tissue types for analysis

Statistical Analysis

Comparison of survivors and deceased individuals was performed at 3-, 6- and 12-month postoperatively. For univariable analysis, the Mann-Whitney U test was used for continuous variables and the χ^2 analysis was used for categorical variables. At each timepoint, we then performed a stepwise, multivariable, logistic regression, using criterion P-values of $P < 0.30$ for inclusion and $P > 0.15$ for exclusion. The inclusion criterion was selected to select for only variables with reasonable correlation to survival on univariate analysis and an exclusion value of $P>0.15$ was chosen to build a model with the strongest predictive power from all included variables. The motivation behind this was to identify additional independent predictors that could serve to enhance existing prognostic scales. Receiver operating curve (ROC) curves were constructed for the final models to examine the degree to which the model fit the existing data.

Results

Demographics

Of the 333 patients in our database, CT scans were available for 98 patients. Of the 333 patients, 235 were excluded because we were unable to obtain preoperative CT abdomen/pelvis scans obtained within 3 months of surgery. However, one patient was excluded, as prior instrumentation at the L3/4 level created an artifact that rendered it unreadable by the WEKA software. This left 97 patients, of whom 75 had complete follow-up and medical records. Descriptive statistics of the cohort with full data (Table 1) are shown below; these patients were grossly similar to the full cohort with respect to mean age (58.2 vs. 56.5 y), sex (60.2% vs. 57.3% male), race (66.3% vs. 66.7% white), BMI (25.3 vs. 26.0 kg/m2), body morphometry parameters, heath comorbidities (modified CCI, 2.00 vs. 1.84), Tomita score (6.52 vs. 6.71), and Tokuhashi score (6.77 vs. 6.89). Median overall survival for the cohort with complete follow-up was 160 days (range: 4–2672 d), with 3-, 6-, and 12-month survivals of 65.3%, 45.3%, and 24.0%, respectively. Five from this cohort were alive at the time of our analysis.

Table 1 Demographic Data for Patients with Complete Follow-Up (n = 75)

Variable	Value
Age	56.5 ± 3.4 years
Sex	57.3% Male
Race	66.7% White 30.7% Black 2.7% Other
Primary Tumor Type	17.3% Lung 14.7% Prostate 12.0% Colorectal 10.7% Breast 9.3% Kidney 4.0% Myeloma 4.0% Nasopharynx 2.7% Lymphoid 2.7% Thyroid 2.7% Testicle 2.7% Sarcoma 2.7% Pancreas 2.7% Salivary Gland 1.3% Unknown 10.7% Other
Time Between Diagnosis of Primary and Spine Metastasis	83.0 ± 65.1 months
Survival	12.7 ± 4.3 months
3 months	65.3%
6 months	45.3%
12 months	24.0%
Spine Level	16.0% Cervical 58.7% Thoracic 25.3% Lumbar
Systemic Disease	
>1 Spine Metastases	66.7%
Visceral Metastases	70.7%
Extravertebral Metastases	50.7% None 49.3% One or more
Functional Status Pre-Operative Ambulatory	78.7%
Frankel Status	76.0% A 16.0% B 6.7% C 1.3% D 0% E
Other Treatment	
Pre-Operative Chemo	78.7%
Post-Operative Chemo	44.0%
Surgery for Primary	64.0%
Modified CCI	1.84 ± 0.19
Greater than 0	84.0%

Variable	Value
Tomita Score	6.71 ± 0.43
Category	18.7% Good 16.0% Moderate 24.0% Poor 41.3% Very Poor
Tokuhashi Score	6.89 ± 0.36
Category	2.7% Good 14.7% Moderate 82.7% Poor
Body Morphometry	
BMI	26.0 ± 1.4 kg/m^2
VFA	11163 ± 2021mm^2
SFA	26043 ± 3529mm^2
VFA/SFA	0.49 ± 0.09
TMA	13746 ± 752mm^2

All means are given as mean ± 95% CI. BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; VFA: visceral fat area; SFA: subcutaneous fat area; VFA/SFA: ratio of visceral fat area to subcutaneous fat area; TMA: total muscle area.

3-Month Overall Survival

On univariable analysis (supplementary table 1), modified CCI (1.6 v. 2.3; p = 0.02), pre-operative Frankel E status (83.7% v. 61.5%; p = 0.03), and postoperative chemotherapy (55.1% v. 23.1%; p = 0.008) were significantly associated with survival. Variables also included in the multivariable analysis were age at surgery ($p > 0.05$), BMI (p = 0.09), Tomita score <4 (p = 0.08), VFA (p = 0.23), and SFA (p = 0.21).

On multivariable analysis (Table 2), only VFA [odds-ratio (OR) = 1.12 per 1000mm^2; 95% CI: 1.02-1.23; p = 0.02] significantly predicted 3-month survival. We observed on linear regression that VFA had a moderate (r = 0.56), yet highly significant correlation with BMI ($p < 0.0001$), as did SFA (r = 0.87; $p < 0.0001$), but these latter 2 variables had weaker associations with 3-month survival and were not significant in the multivariable model (Figs. 2A-D). Other variables included in the final model were primary tumor location (P = 0.08-0.84), pre-operative Frankel status (P = 0.08), post-operative chemotherapy use (p = 0.06), modified CCI ($p > 0.05$), and a Tomita score <4 (p = 0.07). Construction of a ROC (Fig. 3A) for the model showed a good fit for the data, with c-statistic of 0.8312. To further emphasize the superiority of VFA, we constructed an identical model with BMI in place of VFA and found that it had inferior diagnostic characteristics (c-statistic of 0.8124; not shown).

Table 2 Multivariable Logistic Regression for 3-Month Overall Survival

Variable	OR	95% Confidence Interval		p-value
		Lower Limit	*Upper Limit*	
VFA (per 1000mm^2)	1.12	1.02	1.23	0.02
Tumor Type				
Breast	Ref			
Kidney	0.24	0.05	1.20	0.08
Lung	1.16	0.27	4.93	0.84
Other	2.04	0.73	5.73	0.18
Prostate	0.57	0.09	3.41	0.54
Frankel (E v. A-D)	1.97	0.92	4.24	0.08
Post-Op Chemo	1.97	0.98	3.96	0.06
Modified CCI	0.55	0.30	1.00	>0.05
Tomita < 4	3.13	1.10	10.78	0.07

CCI: Charlson Comorbidity Index; VFA: visceral fat area

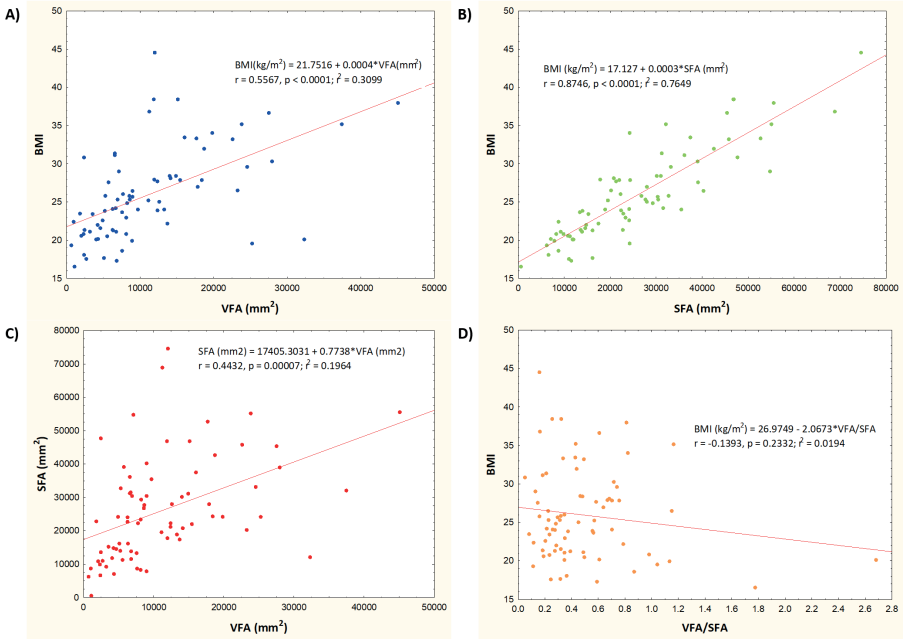

Figure 2
Linear regressions showed a significant correlation between VFA and BMI (A), SFA and BMI (B), and VFA and SFA (C). D, No significant correlation was noted between BMI and the ratio of visceral to subcutaneous fat. BMI indicates body mass index; SFA, subcutaneous fat area; VFA, visceral fat area.

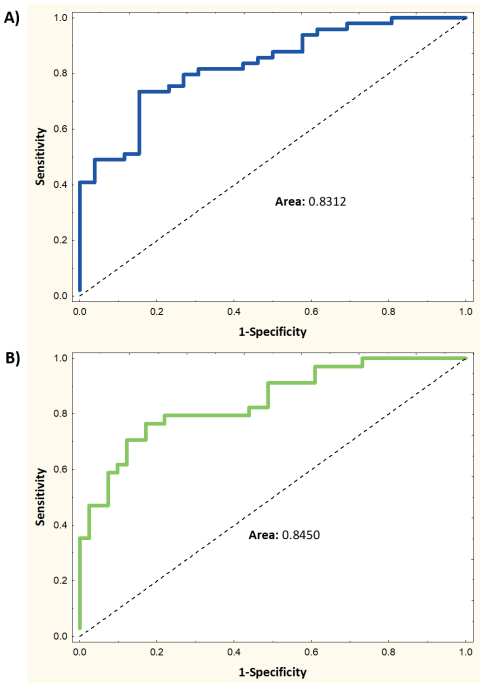

Figure 3. Receiver operating curves for models predicting survival at 3 (A) and 6 months (B) postoperatively.

6-Month Overall Survival

Factors significantly associated with 6-month overall survival (Supplementary table 1) included postoperative chemotherapy use (58.8% v. 31.7%; p = 0.02), having a lower modified CCI (1.5 vs. 2.1; p = 0.03), BMI (28.0 v. 24.3kg/m^2; p = 0.002), and having a higher subcutaneous fat area (31,278 v. 21,701mm^2; p = 0.002). Other variables included in the multivariable analysis were age at the time of surgery (p = 0.10), race (p = 0.25), primary tumor type (p = 0.22), presence of extra vertebral bone metastases (p = 0.13), preoperative ambulatory status (p = 0.07), KPS (p = 0.09), and VFA (p = 0.12).

On multivariable analysis (Table 3), BMI (OR = 1.19 per kg/m^2; 95% CI: 1.04-1.35; p = 0.009), KPS (OR = 1.07 per point; [1.00-1.15]; p < 0.05), modified CCI of 0 vs. >0 (OR = 2.97; [1.12-7.91]; p = 0.03) and postoperative chemotherapy use (OR = 2.31; [1.13-4.71]; p = 0.02) were all significantly associated with 6-month overall survival. Also included in the final model were primary tumor type (p = 0.06-0.70), preoperative Frankel E status (p = 0.10), and preoperative ambulatory status (p = 0.11). The ROC curve showed that this model fit the data with good strength (Fig. 3B), as the c-statistic was 0.8450.

Table 3. Multivariable Logistic Regression for 6-Month Overall Survival

Variable	OR	95% Confidence Interval		p-value
		Lower Limit	*Upper Limit*	
BMI (per kg/m2)	1.19	1.04	1.35	0.009
KPS (per point)	1.07	1.00	1.15	<0.05
Tumor Type				
Breast	Ref			
Kidney	0.70	0.12	3.90	0.68
Lung	0.15	0.02	1.12	0.06
Other	2.40	0.85	6.79	0.10
Prostate	1.36	0.29	6.51	0.70
Ambulatory Pre-Op	2.01	0.85	4.77	0.11
Frankel (E v. A-D)	0.43	0.15	1.17	0.10
Modified CCI (0 v. >0)	2.97	1.12	7.91	0.03
Post-Op Chemo	2.31	1.13	4.71	0.02

BMI: body mass index; KPS: Karnofsky performance status; CCI: Charlson Comorbidity Index; OR: odds ratio; Ref: reference.

12-Month Overall Survival

Three factors were found to be significantly associated with 12-month overall survival on univariable analysis (Supplementary Table 1). These were BMI (29.0 v. 25.0kg/m^2; p = 0.007), postoperative chemotherapy use (66.7% v. 36.8%; p = 0.03) and SFA (34,453 v. 23,387mm^2; p = 0.003). Subsequently, a multivariable analysis was performed using the before mentioned factors. This multivariable analysis, however showed signs of overfitting and was therefore regarded as unreliable. This outcome was not unexpected given the patients' low survival rates.]

Discussion

In the overwhelming majority of cases, operations for patients with spinal metastases are palliative, not curative.[7,8] Given that these surgeries are performed to improve a patient's quality of life, surgical candidacy hinges heavily upon the expectation that the patient will survive surgery and recover quickly enough to enjoy an improved quality of life. Multiple scales, including those of Tomita and Tokuhashi, have been derived in order to predict survival in this patient population, with the goal of distinguishing patients who will derive meaningful benefit from surgical intervention from those who will not.[27,28] These scales incorporate several factors, including preoperative functional status, extent of systemic disease, and primary tumor type. However, none of these

scales incorporates assessments of the patient's overall state of health, including markers of cachexia and sarcopenia.

Cachexia, the chronic wasting seen in 50-80% of oncology patients, has previously been correlated with overall survival in patients with a number of different primary pathologies.[11–19,29] These studies have utilized routine imaging — the L3/4 slice of standard CT abdomen volumes — to radiographically quantify cachexia, which is seen as decreases in muscle cross-sectional area, VFA, and SFA.[30–33] All 3 metrics have been previously associated with survival in oncology patients, with TMA and SFA being positively correlated with survival in the majority of studies.[11,14,17,19,34–36] The results surrounding visceral fat volume have been more controversial, with some studies demonstrating a negative association with overall survival, and others showing a positive association with overall survival, as was seen for 3-month survival in the present study.[13,20–22,37,38] In addition, yet other studies have proposed that it is the ratio of visceral to subcutaneous fat area VFA/SFA that portends a poor prognosis in primary solid malignancies.[39,40] However, this ratio was nog predictive of short-term survival in the current study.

The reason for the heterogeneity in the findings on VFA and survival may stem from an interaction between the body's metabolic state and the extent of tumor dissemination. One study suggesting this was recently published by Park and colleagues, who reported the results of a retrospective cohort of 186 in-patients undergoing surgical resection of colon cancer with regional lymphadenectomy.[22] For each patient, VFA, SFA, and TMA were evaluated on a standard pre-operative CT volume using the L3/4 (umbilical) axial plane. In addition, resection samples were assessed for the number of involved and uninvolved lymph nodes, which was then converted into a ratio of lymph node involvement, a metric used by the investigators as a proxy for the extent of disease dissemination. Using these data, the researchers found that increased VFA had an independent, negative association with lymph nodes involvement [hazard ratio (HR) = 0.291; 95% CI: 0.133-0.638; P = 0.002], suggesting that visceral obesity was a negative predictor of tumor spread. Furthermore, mean overall survival was significantly longer in patients with predominantly visceral fat adiposity, suggesting that visceral obesity might serve as a protective factor in this category of patients with locally-advanced disease.

This result is similar to that obtained by Rickles et al., who reported the results of a retrospective series of 219 patients with colorectal cancer undergoing surgical resection.[23] In their study, Rickles and colleagues used volumetric analysis software to calculate the volume of visceral fat and subcutaneous fat on a standard preoperative CT. They observed that visceral fat volume was not a significant predictor for the overall cohort, however, it became significant when the group was divided based upon disease stage. In patients with more localized

disease (stage II), visceral fat was negatively associated with overall post-operative survival (HR = 1.97; 95% CI: 0.78-5.02; p = 0.154), disease-free survival (HR = 2.72; 1.21-6.10 ; p = 0.015), and recurrence-free survival (HR = 3.76; 1.12-12.57 ; p = 0.032). By contrast, in patients with advanced disease (stage III), visceral fat was positively associated with all three outcomes: overall post-operative survival (HR = 0.43; 0.17-1.07; p = 0.069), disease-free survival (HR = 0.50; 0.23-1.06; p = 0.071), and recurrence-free survival (HR = 0.39; 0.16-0.99; p = 0.046).

Given these results, as well as those of our own, which were obtained from a cohort comprised entirely of stage IV patients, we propose that visceral fat may function as a double-edged sword in oncology patients. For those with localized, early-stage disease, prognosis is often very good, with 5-year expected survivals in excess of 90% for many pathologies, including breast, prostate, and colorectal. [41] Accordingly, the causes of mortality in this patient population may be similar to those in the general population.[42–44] Within the healthy population, abdominal obesity has been positively associated with all-cause mortality, and so logically we would expect it to be negatively associated with survival in patients with early-stage disease.[45] To support this, univariable logistic regressions of BMI against survival at 3-, 6-, and 12-month time show increasing area under the curve with progressively longer timepoints: c-statistic: 0.6185, 0.7080, and 0.7124, respectively (not shown).

By contrast, in patients with advanced disease, such as those in our cohort, the cause of death is most likely to be related to the oncologic disease itself.[42–44] Within this cohort, having larger levels of visceral fat may reflect a superior baseline metabolic status, as these patients are still able to absorb the calories necessary to generate visceral fat. Consequently, the visceral fat serves as a marker for superior baseline health and greater energy reserves with which to combat the progressive deterioration seen in end-stage patients.[46] If such were the case, we would expect that visceral fat mass is a protective factor only in the end-stages of disease, which is consistent with our finding that VFA was significantly associated with survival at 3-, but not at 6- or 12-months postoperatively.

The advantage of VFA as a marker, is that it may allow surgeons to better evaluate the cohort of patients in whom surgical intervention is most controversial – those with limited survival. It takes advantage of imaging modalities that are both easily acquired and part of the current standard of care. In addition, it does not repeat any of the risk factors utilized by current predictive scales, which means that it could potentially serve as an adjunct to existing metrics. This reliance on objective, computer-measured metrics also means that it could easily be incorporated into computer-based algorithms that are becoming increasingly popular in spine surgery.[47]

Limitations of this study include its retrospective nature and the limited number of patients with imaging data available for analysis. While our sample size is small relative to other case series, it is similarly sized to other reports on the prognostic value of body morphometry, including those of Ladoire et al. and Antoun et al. and is therefore similarly powered.[15,34] It is impossible to calculate the actual power of our results though, as no prior literature exists for our specific patient population, and therefore we are unable to generate an estimate of the population difference. In addition, the long duration of the inclusion window means that significant changes in adjuvant therapy regimens are likely to have occurred between the oldest and newest cases.

These changes could not be accounted for in our analysis. Further research is necessary to verify our model on larger cohorts and to evaluate the influence of changes in radiotherapy and chemotherapy on patient prognosis. Lastly, our study identified predictors of survival using logistic regression as opposed to Cox Hazards regression. The reason for our decision was that we were specifically interested in factors predicting survival to the 2 timepoints most commonly cited as dividing surgical from nonsurgical candidates—3- and 6-month postsurgery. In future analysis we propose to conduct Cox Hazards regression to identify predictors over overall survival.

Conclusions

Accurate prediction of postoperative survival is a key component in the determination of the appropriateness of surgery in patients with spinal metastases. Previous predictive scales have failed to incorporate assessments of cachexia, which has been shown to be significantly associated with overall survival. Here, we demonstrate that visceral fat mass, as assessed using a standard-of-care abdominal CT image, is a positive predictor of short-term postoperative survival in patients with spinal metastases. Consequently, optimal patient selection may be enhanced by considering patient adipopenia in additional to scores on current predictive scales.

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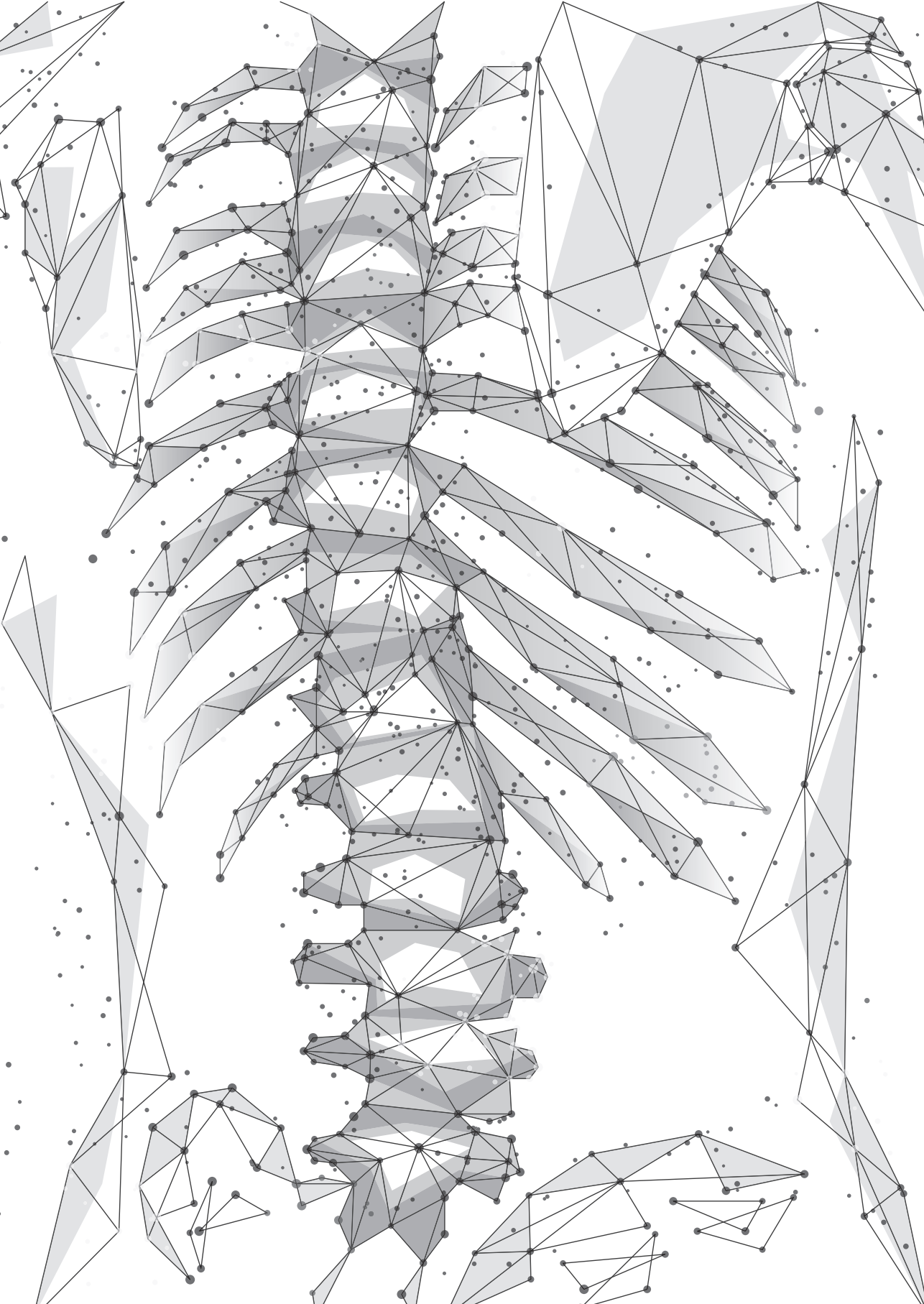
Supplementary Table 1. Univariable Analysis of 3-month, 6-month, and 12-month Overall Survival

Variable	Status at 3-month Follow-Up		p	Status at 6-month Follow-Up		p	Status at 12-month Follow-Up		p
	Alive	Deceased		Alive	Deceased		Alive	Deceased	
Total Number	49	26		34	41		18	57	
Sex (Male)	57.1%	57.7%	0.96	52.9%	61.0%	0.48	44.4%	61.4%	0.20
Age at Surgery	54.4 ± 3.2	60.6 ± 3.7	>0.05	53.3 ± 3.4	59.2 ± 3.4	0.10	57.4 ± 3.3	56.3 ± 3.5	0.75
BMI (Mean)	26.7 ± 1.4	24.5 ± 1.4	0.09	28.0 ± 1.3	24.3 ± 1.3	0.002	29.0 ± 1.4	25.0 ± 1.3	0.007
	65.3% White	69.2% White		67.7% White	65.9% White		61.1% White	68.4% White	
Race	30.6% Black	30.8% Black	0.58	26.5% Black	34.1% Black	0.25	33.3% Black	29.8% Black	0.64
	4.1% Other	0% Other		5.9% Other	0% Other		5.6% Other	1.8% Other	
	10.2% Lung	23.1% Lung		5.9% Lung	22.0% Lung		11.1% Lung	15.8% Lung	
	14.3% Prostate	15.4% Prostate		17.6% Prostate	12.2% Prostate		16.7% Prostate	14.0% Prostate	
Primary Tumor	14.3% Breast	3.9% Breast	0.22	14.7% Breast	7.3% Breast	0.22	22.2% Breast	7.0% Breast	0.24
	6.1% Kidney	15.4% Kidney		5.9% Kidney	12.2% Kidney		0% Kidney	12.3% Kidney	
	55.1% Other	42.3% Other		55.9% Other	46.3% Other		50.0% Other	50.9% Other	
Time Between Primary and Spinal Met Diagnosis	57.0 ± 14.2	131.9 ± 109.4	0.47	58.5 ± 13.8	103.2 ± 87.4	0.34	66.5 ± 16.1	88.2 ± 74.3	0.45
	14.3% Cervical	19.2% Cervical		14.7% Cervical	17.1% Cervical		11.1% Cervical	17.5% Cervical	
Spinal Level	59.2% Thoracic	57.7% Thoracic	0.84	58.8% Thoracic	58.5% Thoracic	0.95	61.1% Thoracic	57.9% Thoracic	0.81
	26.5% Lumbar	23.1% Lumbar		26.5% Lumbar	24.4% Lumbar		27.8% Lumbar	24.6% Lumbar	
Systemic Disease									
>1 Spine Met	65.3%	69.2%	0.73	67.7%	65.9%	0.87	72.2%	64.9%	0.57
Visceral Met	69.4%	73.1%	0.74	70.6%	70.7%	0.99	66.7%	71.9%	0.67
Extravertebral Bone Met	53.1%	42.3%	0.38	58.8%	41.5%	0.13	61.1%	45.6%	0.25
Pre-Op Functional Status									
Ambulatory	81.6%	73.1%	0.39	88.2%	70.7%	0.07	94.4%	73.7%	0.06
Frankel E	83.7%	61.5%	0.03	82.4%	70.7%	0.24	83.3%	73.7%	0.40
Modified CCI	1.6 ± 0.3	2.3 ± 0.2	0.02	1.5 ± 0.3	2.1 ± 0.2	0.03	1.9 ± 0.27	1.8 ± 0.3	0.83
Modified CCI > 0	77.6%	96.2%	0.04	73.5%	92.7%	0.02	83.3%	84.2%	0.93
Other Treatment									
Preop Chemotherapy	79.6%	76.9%	0.79	82.4%	75.6%	0.48	72.2%	80.7%	0.44
Postop Chemotherapy	55.1%	23.1%	0.008	58.8%	31.7%	0.02	66.7%	36.8%	0.03
Surgery for Primary	63.3%	65.4%	0.86	58.8%	68.3%	0.40	55.6%	66.7%	0.39
Good Tomita Score	24.5%	7.7%	0.08	23.5%	14.6%	0.33	27.8%	15.8%	0.26
Good Tokuhashi Score	2.0%	3.9%	0.64	2.9%	2.4%	0.89	5.6%	1.8%	0.38
Morphometric Parameters									
VFA (mm^2)	12203 ± 2183	9200 ± 1619	0.23	13115 ± 2313	9543 ± 1683	0.12	11603 ± 1639	11023 ± 2140	0.44
SFA (mm^2)	27849 ± 3683	22637 ± 3139	0.21	31278 ± 3401	21701 ± 3354	0.002	34453 ± 3420	23387 ± 3366	0.003
VFA/SFA	0.51 ± 0.10	0.46 ± 0.08	0.69	0.45 ± 0.07	0.52 ± 0.11	0.62	0.37 ± 0.05	0.53 ± 0.10	0.11
TMA (mm^2)	13838 ± 807	13572 ± 647	0.95	13833 ± 847	13674 ± 674	0.89	13448 ± 636	13840 ± 789	0.76
KPS	74.9 ± 2.8	71.5 ± 3.0	0.37	77.1 ± 2.6	71.0 ± 3.0	0.09	77.2 ± 2.6	72.6 ± 3.0	0.34

Legend: SFA = subcutaneous fat area; TMA = total muscle area; VFA = visceral fat area; VFA/ SFA = ratio of visceral fat area to subcutaneous fat area
Note: p-values represent Chi-Square for categorical variables and Mann-Whitney U test for quantitative



CHAPTER 4

Pain response after stereotactic body radiation therapy versus conventional radiotherapy in patients with bone metastases – a phase II, randomized controlled trial within a prospective cohort

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Abstract

Background: Pain response after conventional external beam radiotherapy (cRT) in patients with painful bone metastases is observed in 60–70% of patients. The aim of the VERTICAL trial was to investigate whether stereotactic body radiotherapy (SBRT) improves pain response.

Methods: This single center, phase 2, randomized controlled trial was conducted within the PRESENT cohort, which consists of patients referred for radiotherapy of bone metastases to our tertiary center. Cohort participants with painful bone metastases who gave broad informed consent for randomization, were randomly assigned to cRT or SBRT. Only patients in the intervention arm received information about the trial, and were offered SBRT (1x18 Gy, 3x10 Gy, or 5x7 Gy) which they could accept or refuse. Patients who refused SBRT underwent standard cRT (1x8 Gy, 5x4 Gy or 10x3 Gy). Patients in the control arm were not informed. Primary endpoint was pain response at 3 months after radiotherapy. Secondary outcomes were pain response at any point within 3 months, mean pain scores, and toxicity. Data was analyzed intention to treat (ITT) and per protocol (PP). This trial was registered with Clinicaltrials.gov, NCT02364115.

Findings: Between Jan 29, 2015, and March 20, 2019, 110 patients were randomized. ITT included 44 patients in the cRT arm and 45 patients in the SBRT arm. In the intervention arm, 12 patients (27%) declined SBRT and 7 patients (16%) were unable to complete the SBRT treatment. In ITT, 14 of 44 patients (32%, 95% CI 18–45%) in the control arm, and 18 of 45 patients (40%, 95%CI 26–54%) in the SBRT arm reported a pain response at 3 months (p=0.42). In PP, these proportions were 14 of 44 (32%, 95%CI 18–45%) and 12 of 23 (46%, 95%CI 27–66%), respectively (p=0.55). In ITT, a pain response within 3 months was reported by 30 of 44 control patients (82%, 95% CI 68%-90%), and 38 of 45 patients (84%, 95% CI 71%-92%) in the SBRT arm. (p=0.12). In PP, these proportions were 36 of 44 (82%, 95% CI 68%-90%) and 26 of 27 (96%, 95% CI 81%-100%) respectively, p=0.12. No grade 3 or 4 toxicity was observed in either arm.

Conclusions: SBRT did not significantly improve pain response in patients with painful bone metastases. One in 4 patients preferred to undergo cRT over SBRT and one in 5 patients starting SBRT was unable to complete this treatment. Due to this selective drop-out, which can be attributed to the character of the intervention, the trial was underpowered to detect the prespecified difference in pain response

Introduction

Bone metastases are a common manifestation of advanced cancer, causing pain and neurologic complaints or deficits, and they often impair overall quality of life [1,2] Palliative radiotherapy (RT) is a proven effective and widely accepted treatment modality for metastatic bone pain.[3,4] Pain response after conventional radiotherapy (cRT) is similar in patients treated with single fraction (8 Gy in a one fraction) and multifraction (20–30 Gy in 5–10 fractions) RT. [1,5,6] It has been suggested that dose escalation and, more specifically, dose escalation per fraction, could improve pain response in patients with metastatic bone pain. [7] Dose escalation using cRT is challenging because surrounding tissues such as the spinal cord have limited tolerance to radiation. Stereotactic body RT (SBRT) allows for accurate administration of a higher dose to the target area, while sparing the surrounding tissue.

Previous studies have shown that SBRT can safely be administered to patients with bone metastases.[7,8] Recent randomized controlled trials (RCTs) comparing the proportion of patients reporting a pain response after cRT versus SBRT show inconsistent results. [9–11] Nguyen et al compared single fraction SBRT to multifraction cRT[9], and found that pain response after SBRT was superior to multifraction cRT at 2 weeks and at 3 months. The recently presented RTOG 0631 trial however, showed no difference in pain response between single fraction cRT (8 Gy) and single fraction SBRT (16–18 Gy). [11]

The VERTICAL trial was designed according to the Trials within Cohorts (TwiCs) methodology with the aim to estimate whether SBRT leads to superior pain response compared to standard cRT in patients with painful bone metastases. In addition, the TwiCs design allowed us to evaluate acceptability and tolerability of SBRT in routine clinical practice.

Methods and Materials

Study design

VERTICAL was a single-center, pragmatic phase 2 RCT conducted within the PRESENT cohort.[12] The VERTICAL study followed the Trials within Cohorts (TwiCs) design, also known as the cohort multiple RCT design.[13] All patients with bone metastases referred to the departments of radiation oncology or orthopedic surgery at our tertiary referral center are systematically invited to participate in the prospective, observational PRESENT cohort. At enrolment in PRESENT, patients give informed consent to the use of their clinical and outcome data for research purposes. Optionally, they provide additional consent to fill out Patient Reported Outcomes (PROs) at regular intervals during follow-up. In addition, in a separate question, we ask patients for their broad consent to be randomized in (near) future RCTs

conducted within the cohort. Patients are informed that randomization means that, when meeting in- and exclusion criteria for future trials, they will be randomized; when randomized to the intervention arm, they will be offered the experimental intervention, which they can accept or refuse. They are also informed that, when assigned to the control arm, they will not be notified about the trial and that their clinical, outcome and PROs data may be used comparatively. [14]

Patients

For the present study, all patients eligible for the VERTICAL trial were identified within PRESENT. Inclusion criteria included histologic proof of malignancy, radiological or histological evidence of bone metastases, no more than two painful lesions requiring treatment, no compression of spinal cord/cauda equina, no or mild neurological signs such as (radiating) pain or numbness, Karnofsky Performance Scale >50 points, and pain score ≥3. Exclusion criteria included contraindications to undergo magnetic resonance imaging (MRI), metastasis from a highly radiosensitive tumor (e.g. lymphoma), lesions too large for SBRT (i.e. >10 cm), estimated life expectancy less than 3 months, previous cRT or SBRT on the same level, need for surgical stabilization, and severe, worsening or progressive neurological deficits (e.g. example muscle weakness). Patients were only eligible when they provided informed consent to filling out PROs and when they gave broad informed consent for future randomization.

At the initiation of the study in January 2015, only patients with vertebral metastases were eligible. From November 17, 2015, onwards, patients with bone metastases at any location were eligible, with the exception of the first and second cervical vertebrae due to proximity of major neurovascular structures. All patients provided written informed consent before enrolment in PRESENT, and all patients in the intervention arm of the VERTICAL study provided additional informed consent to the VERTICAL trial. Approval of the protocol was obtained from the local ethics committee.

Randomization and masking

PRESENT participants meeting the inclusion criteria were randomly assigned (1:1) to receive cRT or SBRT, using block randomization with alternating block sizes. No stratification factors were used and the random allocation sequence was masked. Following the TwiCs methodology, only patients who were randomized to the intervention arm were informed about the VERTICAL trial and were offered SBRT. Additional informed consent was obtained from patients who accepted the offer. Patients who declined the offer received standard cRT. Treatment group allocation was not masked to the investigators or the patients in the intervention arm, but the patients randomized to the control arm were not informed about the VERTICAL trial and received standard cRT.

Procedures

Patients in the cRT arm typically received 8 Gy in 1 fraction; however, a multifraction regime of 20 Gy in 5 fractions or 30 Gy in 10 fractions could be used for patients in good clinical condition as assessed by the radiation oncologist. Single or multiple computed tomography (CT)-guided conformal fields were used for RT planning, in which the clinical target volume (CTV), which included the macroscopic tumor, received at least 80% of the prescribed dose. In 3 patients, Volumetric Modulated Arc Therapy (VMAT) was used to deliver the conventional dose. No immobilization devices were used. Patients undergoing SBRT were immobilized using a vacuum cushion ((BlueBAG™, Elekta, Stockholm, Sweden) or a thermoplastic mask depending on localization. A planning CT (1-mm slice thickness) was acquired and rigidly registered to a dedicated planning MRI (in treatment position), and recent diagnostic positron emission tomography (PET) scan was coregistered if available. The radiation oncologist contoured the gross tumor volume (GTV), referred to as the boost (GTVb); the CTV, referred to as elective CTV (CTVe); and relevant organs at risk. The GTVb was defined as the macroscopic extent of the tumor on all available imaging modalities. The CTVe was generated using a 1.5-cm isotropic margin around the GTVb, excluding soft tissues (bone only); potential extraosseous disease was included in the CTVe. For spinal metastases, the whole vertebra was considered the CTVe. Both the GTVb and the CTVe were expanded with a 2-mm isotropic margin to generate planning target volume margins [15] The planning target volume was prescribed for 18 Gy in a single fraction, 30 Gy in 3 fractions, or 35 Gy in 5 fractions using (VMAT) both with 3 fractions per week. A more detailed protocol for cRT and SBRT planning procedures was published earlier.[16]

From all PRESENT patients, demographic and clinical data as well as treatment characteristics and follow-up data were collected at baseline, before the start of RT, and until death. Because VERTICAL was executed within PRESENT, these data were available for the patients included in the VERTICAL trial. For the VERTICAL trial, data collected at baseline, 2, 4, 6 and 8 weeks and 3 months after treatment was used. Patients completed the Brief Pain Inventory (BPI) combined with a form on (opioid) analgesic use. In addition, (change in) QOL was assessed using the EORTC-QLQ-C15-PAL and EORTC-QLQ-BM22. Here, only the global QOL scores of the QLQ-C15-PAL questionnaire are presented. Detailed analysis of all QOL domains of the QLQ-C15-PAL and QLQ-BM22 questionnaires will be published separately. From the opioid analgesic use, an Oral Morphine Equivalent Dose (OMED) in mg was calculated. When patients failed to return questionnaires, they were systematically reminded by a call from the research team. Patients were asked to fill out the questionnaire, and pain scores and opioid analgesic use were already noted during that call.

Outcomes

The primary endpoint of the VERTICAL trial was the proportion of patients reporting a pain response at 3 months following RT, measured with the BPI, and classified according to the international consensus on palliative RT.[4] Complete response (CR) was defined as a pain score of 0 on a scale from 0 to 10, without increase in pain medication. Partial response (PR) was a decline of at least 2 points or decline of an OMED of at least 25% or both. Pain progression (PP) was an increase of at least 2 points without change in OMED dose, or 1-point increase with an increase of 25% in OMED use. All other pain responses were categorized as indeterminate response (IR). Patients with a complete response or partial response were considered responders, patients with other outcomes were considered non-pain-responders. Patients of whom a pain score was unknown were considered non-pain-responders at that time point. Secondary endpoints were best pain response in the first 3 months after treatment, mean pain scores, OMED use, global QOL, and toxicity in the first 3 months after treatment. Global QOL was rated on a 7-point scale ranging from "very poor" to "excellent". In accordance with the scoring manual, the scale was converted into a score ranging from 0 to 100, with higher scores indicating better QOL [17–19]. Toxicity was assessed by a physician at clinical or telephone follow-up and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Only adverse events grade 3 were recorded because of the high number of study-unrelated adverse events, owing to the natural course of disease in patients with stage IV cancer. By applying the TwiCs design, patients' preferences to undergo SBRT could be estimated, as patients allocated to the intervention arm could accept or refuse the offer of SBRT. Patient-reported reasons for not accepting SBRT were recorded.

Statistical Analysis

We assumed the proportion of patients with pain response at 3 months to be 60% following cRT versus 85% after SBRT. In order to achieve an 80% power and an one-sided α of 5%, 49 patients needed to be enrolled in each arm.[20,21] We assumed that 10% of the patients in the intervention arm would refuse when offered SBRT . We also assumed 100% compliance in the control arm, since control patients were not informed of the SBRT intervention and underwent treatment as usual. In addition, a 10% drop-out was anticipated in both arms, resulting in a total of 55 patients required for each arm.[16]

The proportions of patients reporting a pain response at 3 months (primary endpoint) were compared between the control- and the intervention arms using the Chi-square test. The primary analysis was by intention to treat (ITT), who were found to be ineligible after randomization. Patients in the intervention arm who preferred to undergo cRT when SBRT was offered, and those who did not want to undergo any treatment at all were included in the ITT analysis.

We also conducted a per protocol (PP) analysis and included patients who completed the treatment planned according to the random allocation. In the ITT and PP analyses, patients who did not return their questionnaires were considered nonepain-responders. In addition, a third analysis, a complete case ITT analysis, was performed, in which we analyzed only patients whose response could be assessed at 3 months (alive and responding to questionnaire).

The proportions of patients reporting pain response at at least 1 of the follow-up time points up until 3 months following treatment (secondary outcome) were compared by ITT and PP analyses using the χ^2 test.

The independent samples *t* test was used to compare changes in mean pain scores and OMED use between baseline and follow-up at 3 months relative to baseline by treatment arm. In addition, a linear mixed model analysis was performed to compare mean pain scores adjusted for covariates. Global QOL was analyzed using a mixed model for repeated measures, including time, treatment group and its interaction, and adjusting for baseline QOL scores. Toxicity was assessed in all enrolled patients who received at least 1 RT fraction. Data were analyzed using SPSS, IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. [22]

This trial was registered under NCT02364115.

Role of the funding source

The study was funded by internal sources. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between January 29, 2015 and March 20, 2019, 1102 patients with (painful) bone metastases were included in the PRESENT cohort at our department for RT. Of these patients, 178 patients were eligible (meeting the inclusion and exclusion criteria of VERTICAL). The majority of patients were not eligible for the VERTICAL study because 3 or more locations were treated with RT or were patients had oligometastatic disease, which was treated with SBRT. In addition, patients were often excluded when the metastasis was >10 cm, and/or because there was an increased fracture risk. Of the 178 eligible patients, 42 did not want to participate in the PRESENT cohort, and could not be included in VERTICAL. Seven patients did not provide informed consent for completing PROs, and 7 patients refused future randomization. Ten patients were not randomized because treatment in the intervention arm would not be possible within 10 days, which was considered unethical. The remaining 110 (61%) were randomized (Figure 1).

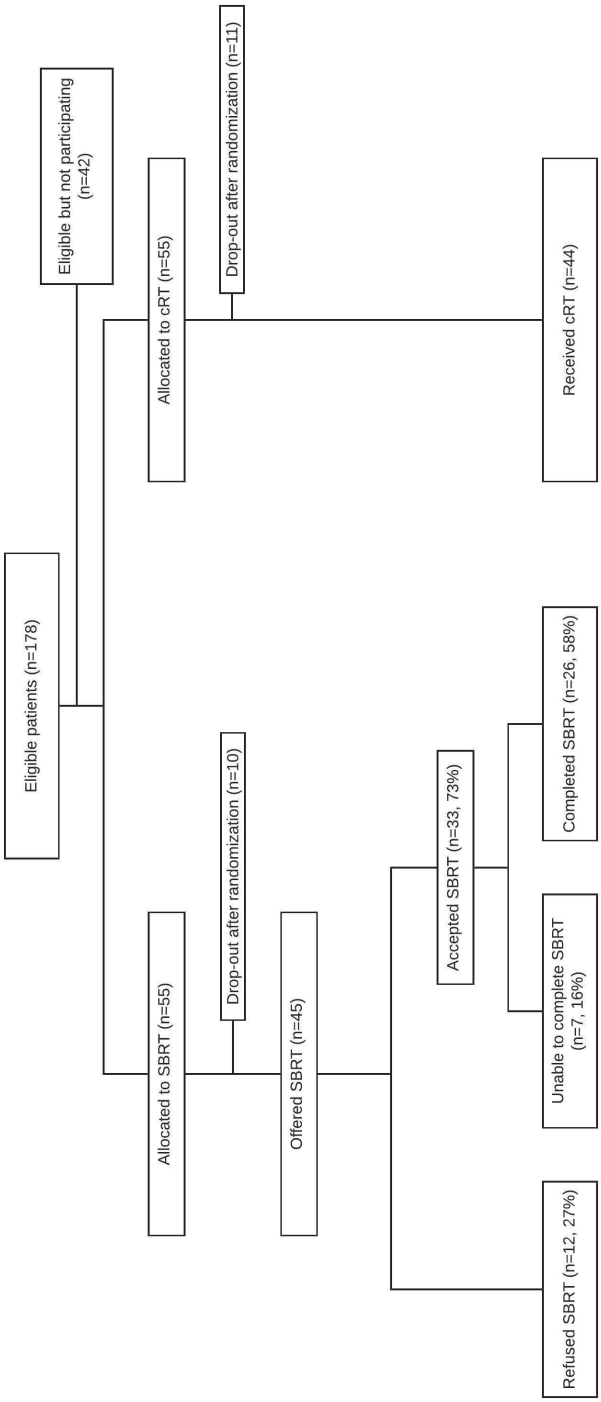

Figure 1. Flowchart of patient enrolled in the VERTICAL trial and treatment allocation.

After randomization, 11 patients in the cRT arm and 10 patients in the SBRT arm dropped out before start of treatment because they did not, or did no longer, meet the inclusion criteria. The most common reasons for drop out were need for surgery, and lack of pain, although the patient was referred because of painful metastases. As a result, a total of 89 patients were included in the ITT analysis, 44 patients in the standard arm, and 45 patients in the experimental arm. Baseline characteristics are shown in table 1.

After offering SBRT to the 45 patients in the intervention arm, 12 patients (27%, 95% CI= 15%-42%) declined the offer and opted for cRT (Fig. 1). Eight of these patients refused SBRT because of the longer waiting time until treatment of up to 10 days. One patient had previously been treated with cRT and was satisfied with the result, and 1 patient refused SBRT because of worries about the increased vertebral fracture risk after SBRT. Of the SBRT refusing patients, 10 patients underwent cRT and 2 refused any treatment. Patients who refused the SBRT treatment were slightly younger, had more co-morbidities, had a higher percentage of lung cancer and a lower percentage of breast cancer, and a higher pain score than patients who accepted SBRT. They were similar in terms of sex and of location of bone metastases (supplementary table 1).

Of the 33 patients who accepted SBRT, 7 (21%) were unable to complete the treatment, 3 of whom underwent cRT. One patient was injured between consecutive fractions due to a fall and was unable to continue SBRT; 1 patient was unable to undergo a planning MRI due to severe bone pain, 1 patient was in too much pain after the first SBRT fraction, did not respond to dexamethasone, and refused to undergo additional fractions; and1 patient turned out to have 3 lesions on MRI requiring treatment. Two patients had MRI-confirmed rapid tumor or metastasis progression and underwent cRT and one patient deteriorated rapidly and underwent cRT before SBRT could be started. Overall, 44 patients (100%) completed the allocated cRT, and 26 patients (58%) completed the allocated SBRT treatment. Thirteen patients (29%) randomized to the SBRT arm received cRT, and 6 patients did not undergo any treatment.

Fourteen patients died within the three months — 7 patients in the cRT arm and 7 patients in the SBRT arm. Median time to death was 44 days (interquartile range [IQR 29-48 days) in the cRT arm and 46 days (IQR 37-75) in the SBRT arm. The overall 90 day survival was 84% in both arms (supplementary figure). Despite repeated calls, questionnaires response rates were rather low. A total of 35 patients (39%) returned their questionnaires at all follow-up moments, and 77 patients (87%) returned at least one follow up questionnaire (Table 2). The patients in the SBRT arm who did not undergo any treatment did not return any questionnaires. Of the 13 patients who underwent cRT instead of the allocated SBRT, 8 returned at least 1 questionnaire. Patients who did not return a questionnaire, were considered to be a non-pain-responders in at the given moment in follow-up.

Table 1. Baseline characteristics of patients with painful bone metastases enrolled in the VERTICAL trial

	Conventional Radiotherapy group (N = 44)	Stereotactic Body Radiotherapy Group (N = 45)
Male sex, n (%)*	31 (70)	24 (53)
Median age (IQR), y	63 (57-73)	65 (61-72)
Median Charlson Comorbidity Index (IQR)*†	6 (6-7)	6 (6-7)
Karnofsky Performance Status, n (%) *‡		
0-50	1 (3)	2 (6)
60-70	11 (37)	14 (40)
80-100	18 (60)	19 (42)
Primary Tumour Site, n (%)		
Lung	9 (21)	14 (31)
Breast	8 (18)	9 (20)
Prostate	9 (21)	11 (24)
Other[§]	18 (40)	11 (24)
Location bone metastases, n (%)		
Spine	22 (50)	27 (60)
Nonspine	22 (50)	18 (40)
Median pain score at baseline, NRS (IQR)	6.2 (2)	6.6 (1.8)
Pain medication at baseline, n (%) *		
None	7 (16)	7 (16)
Nonopioid	15 (34)	15 (33)
Weak opioid	1 (2)	1 (2)
Strong opioid	21 (48)	22 (49)
Oral morphine equivalent dose —median (IQR)*	60 (40-120)	60 (40-110)
Concomitant systemic treatment	17 (39)	25 (56)
Hormone therapy	7 (16)	11 (24)
Chemotherapy	7 (16)	10 (22)
Targeted therapy	2 (4)	2 (4)
Other	1 (2)	2 (4)

Abbreviations: IQR Z interquartile range; NRS Z Numeric Rating Scale, ranging 0-10.
* Percentages might not add up to 100% because of rounding.
† The scale of the Charlson Comorbidity Index ranges from 0 to 40, where a higher score indicates a worse prognosis. Patients with bone metastases have a score of at least 6.
‡ The Karnofsky performance status score is assessed on a 100-point scale, with lower numbers indicating greater disability.
[§] Conventional external beam radiation therapy arm: kidney (n = 5), bladder (n = 4), colon and rectum (n = 5), esophagus (n = 1), another endocrine (n = 1). Stereotactic body radiation therapy arm: bladder (n = 4), kidney (n = 3), colon and rectum (n = 1), stomach (n = 1), esophagus (n = 1), another upper digestive tract (n = 1)

Table 2. Number and proportion of patients returning their questionnaire (n) of total patients at risk (N).

Treatments arm	At 2 wk	At 4 wk	At 6 wk	At 8 wk	At 3 mo
Conventional external beam radiation therapy arm, n (%)	32 (73%)	33 (77%)	27 (68%)	28 (72%)	23 (62%)
Deceased	0	1	4	5	7
Stereotactic body radiation therapy, n (%)	37 (82%)	36 (80%)	32 (76%)	33 (85%)	31 (82%)
Deceased	0	0	3	6	7

In the ITT analysis, 14 out of 44 patients (32%; 95% CI: 18–45%) in the cRT arm reported a pain response at 3 months compared to 18 out of 45 patients (40%; 95% CI: 26–54%) in the SBRT arm (p= .42). In the PP analysis, 14 out of 44 patients (32%; 95%CI 18–45%) in the cRT arm, and 12 out of 26 patients (46%; 95%CI 27–66%) in the SBRT arm reported a pain response at 3 months, p= .55 (table 3).

In the subset of evaluable (alive and responding) patients (i.e. complete case ITT analysis), 14 out of 23 patients (61%; 95% CI 39-80%) in the cRT arm, and 18 out of 31 patients (58%; 95% CI 39–75%) in the SBRT arm reported a pain response at 3 months, p= .84. (table 3).

Table 3. Patients who perceive a pain response after radiation therapy (n), according to treatment*

Analysis	At 2 wk	At 4 wk	At 6 wk	At 8 wk	At 3 mo
ITT Analysis					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	18/45 (40%)	16/45 (36%)	19/45 (42%)	17/45 (44%)	18/45 (40%)
Per protocol analysis (patients undergoing allocated treatment)					
cRT	19/44 (43%)	19/44 (43%)	13/44 (30%)	16/44 (36%)	14/44 (32%)
SBRT	12/26 (46%)	10/26 (39%)	13/26 (50%)	11/26 (42%)	12/26 (46%)
ITT analysis of evaluable patients†					
cRT	19/32 (59%)	19/33 (58%)	13/27 (48%)	16/28 (57%)	14/23 (61%)
SBRT	18/37 (49%)	16/36 (44%)	19/32 (59%)	17/33 (52%)	18/31 (58%)

Abbreviations: cRT = conventional external beam radiation therapy; ITT = intention to treat; PP = per protocol; SBRT = stereotactic body radiation therapy.
* Presented as n/N (%). Patients are considered to have a response as pain score or analgesic use went down per the international consensus criteria.4 In the ITT and PP analysis, patient who did not return a questionnaire or were deceased were considered nonresponders. In the ITT of analysable patients, only patients who returned a questionnaire were included.
† Number of patients reporting a pain response (n), who returned a questionnaire (N). Presented as n/N (%).

The proportion of patients reporting a pain response on at least one of the follow-up time points following treatment up until 3 months was comparable between both treatment arms in the ITT and PP analyses: 36 out of 44 patients (82%, 95% CI 68%-90%) in the cRT arm versus 38 out of 45 patients (84%, 95% CI 71%-92%) in the SBRT arm (p=0.73) in the ITT analysis. In the PP analysis, 36 out of 44 patients (82%, 95% CI 68%-90%) in the cRT arm versus 26 out of 27 patients (96%, 95% CI 81%-100%) in the SBRT arm reported a pain response within 3 months after treatment (p= .12). Percentage of patients reporting a pain response, at each follow-up point were comparable (Fig. 3).

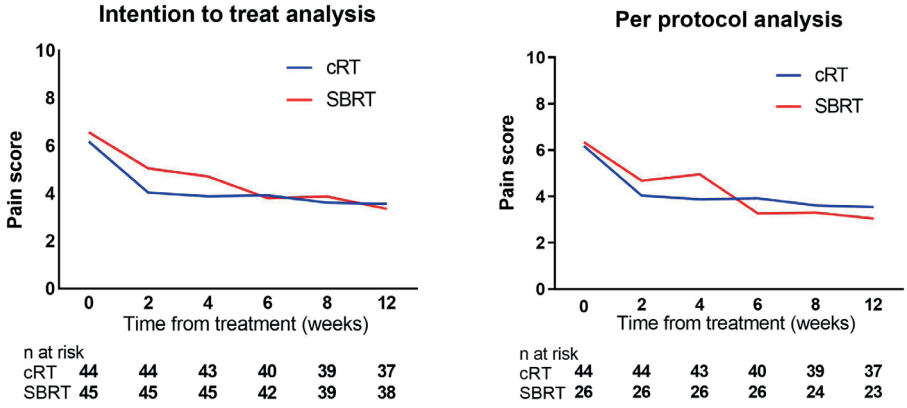

Figure 3. Pain scores during the first 12 weeks after radiation therapy treatment. Pain was scored on a 10-point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). Pain was measured at baseline before radiation therapy treatment and after 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 3 months after radiation therapy treatment

In the ITT analysis, mean pain scores at baseline were 6.2 (standard deviation [SD] = 2.0) in the cRT arm and 6.6 (SD = 1.8) in the SBRT arm (Fig. 1). At 3 months, the mean pain score was 3.6 in the cRT arm (difference -2.5; 95% CI: -3.8 – -1.1) and 3.4 in the SBRT arm (difference -2.9; 95% CI: -4.0 to -1.9; p = .41; Fig. 3). In the PP analysis, the mean pain scores in the cRT remain 6.2 (SD=2.0), since all patients allocated to the control arm underwent the standard treatment. Mean pain score in the SBRT arm at baseline was 6.3 (SD = 1.9) which dropped to 3.0 at 3 months (difference -3.0; 95% CI: -4.36 to -1.72). In A mixed model analysis in which the treatment, interaction between treatment and time and primary tumor were taken into account as fixed effects, no significant difference was found (Supplementary Table 3). At baseline, 22 patients in both arms used opioids with a mean OMED of 83 mg (SD=67) in the cRT arm and 95 mg (SD=60) in the SBRT arm. At 12 weeks, 12 patients in the cRT arm and 13 in the SBRT arm used opioids, with an OMED of 83 mg (SD=102) and 86 mg (SD=45) respectively. No difference was found in global QOL scores between patients in the cRT and SBRT arm (Table 4; p=0.91). No CTCAE

grade 3 or 4 toxicity related to the treatment was reported in either treatment arm within 3 months after RT.

Table 4. Global QoL scores of the EORTC-QLQ-C15 questionnaire*

	Baseline	At 4 wk	At 8 wk	At 3 mo
Conventional external beam radiation therapy	67 (50-67)	67 (50-83)	67 (67-83)	67 (67-83)
Stereotactic body radiation therapy	67 (50-67)	50 (50-67)	67 (50-83)	67 (50-83)

* Presented as median (interquartile range)

Discussion

In this cohort-embedded, randomized controlled trial following the TwiCs design, we found no differences in pain response, pain scores, and global QOL between patients receiving cRT and those (offered to be) treated with SBRT. In both arms, patients had a comparable decrease in pain and analgesic use in the 3 months after treatment. We found that a substantial proportion of patients (27%) preferred to undergo cRT instead of SBRT when given the choice. In addition, a substantial proportion of patients (21%) was unable to complete SBRT treatment, a phenomenon that was not observed in the cRT arm.

Our results are in line with the RTOG 0631 trial, in which no difference in pain response was found between the cRT (58%) and SBRT (40%) group 3 months after RT for spinal metastases.[11] In that trial, 339 patients were randomized 1:2 to cRT or SBRT respectively.[8] In addition our trial also showed mean pain scores similar to those in the RTOG 0631 in which, in the 3 months after RT, mean pain scores decreased from 5.88 to 2.05 in the cRT arm and from 6.06 to 3.06 in the SBRT arm. In addition, the results of Sprave et al. are similar to the results of the RTOG 0631 trial and our results.[10] Sprave et al. performed a classic RCT with 30 patients per arm with spinal metastases receiving either 24 Gy SBRT in 1 fraction or 30 Gy multifraction cRT.[10] In the ITT analysis, no significant difference between cRT and SBRT was found in pain response after 3 months (48% versus 70% respectively, p= .057). Pain scores displayed a similar trend in both treatment arms. Because this trial was small, and therefore underpowered, Sprave et al recommended conducting larger RCTs to find clinically significant differences. A small, 3-arm randomized phase 2 trial by Berwouts et al showed that 8 Gy in a single fraction using fluorodeoxyglucose-based—dose painting resulted in a higher pain response (12/15, 80%) compared to 16 Gy in a single fraction using fluorodeoxyglucose-based—dose painting (9/15, 60%).[23] The authors explained their finding, among other reasons, by reducing the dose to normal tissues. A higher SBRT dose results in a higher dose to normal tissues, actually inducing elevation of inflammatory cytokines, possibly inducing adverse effects after SBRT.[23]

In contrast to the aforementioned studies, as well as ours, Nguyen et al found a significantly better pain response following SBRT (12–16 Gy in 1 fraction) after 2 weeks (for both ITT and PP analyses) and after 3 months (PP analysis). In this trial, the researchers compared 79 patients receiving multifraction cRT with 81 patients receiving SBRT for mainly non—spinal metastases. Pain response rates at 3 months in both arms were low compared to those found in other studies, with 21% in the cRT arm and 38% in the SBRT. Nguyen et al mainly included patients with metastases from lung carcinoma in contrast to the more heterogeneous study population in both the RTOG 0631 trial and our trial. Moreover, the proportion of patients with lung cancer was higher in the cRT arm compared to the SBRT arm (60% and 39%). In previous models predicting pain response, patients with metastases from prostate or breast cancer had a better response than patients with lung cancer.[2,15] The low response rate and homogeneous Nguyen' study group could hamper extrapolation of the results to the general population with bone metastases. The joint result from these trials seems to indicate that dose escalating using SBRT does not lead to better pain response, possibly indicating a much more complex biological reaction of painful bone metastases to irradiation.

To our knowledge, this trial is the first RCT designed according to the TwiCs design in a palliative oncological setting. The TwiCs approach is different from classic RCTs, in which patients are informed about the trial and are asked 3 questions at the same time: (1) whether they are interested in participating in clinical research, (2) whether they agree to be randomized, and (3) whether they are willing to undergo an experimental intervention. In TwiCs, the first 2 questions ("Are you willing to participate in research?" and "Are you prepared to be randomized") are asked at cohort entry, although the last question ("Are you prepared to undergo an experimental intervention") is asked only to patients in the intervention arm (i.e., only to patients who can actually undergo the experimental intervention). This patient-centered, informed consent procedure is less confusing for patients than the standard informed consent procedure in a classic RCT, in which patients receive information about interventions that they may not receive. In addition, the TwiCs approach avoids disappointment of patients allocated to the control arm, considering only patients in the intervention arm receive information about the new intervention. As such, patients in the control arm are not prone to disappointment bias, (i.e. the phenomenon observed among patients randomized to the control arm, while hoping to be randomized to the intervention arm). Because patients know about the availability of a new treatment, not being able to receive the new treatment could induce disappointment and therefore result in reporting a more negative outcome. [24] Avoiding this type of bias is especially attractive in trials assessing a subjective outcome such as pain and QOL.

TwiCs increases efficiency of recruitment.[25,26] We randomized more than 60% of the eligible patients treated for painful bone metastases at our institution during the study period. Similarly high enrolment rates were seen in other TwiCs at our institution, where 63% and 100% of the eligible patients were randomized.[26,27] In classic RCTs in the palliative setting, patient enrolment is challenging. The RTOG0631 trial, for example, took more than 9 years and 65 participating centers to enroll 339 patients (average of 0.6 patients per center per year). A Dutch multicenter classic RCT, the RACOST trial, was stopped early because of slow recruitment.[28,29] We also completed the trial within a single institution in a reasonable time frame of 4 years. As new technologies and treatment options are being developed rapidly, finishing a trial quickly is important.

Patients in the intervention arm decide whether they accept the intervention or not; therefor, the TwiCs approach provides insightful information about the acceptability of the intervention to patients. We found that a rather substantial proportion of patients was not inclined to accept SBRT as a treatment, as 12 patients (27%) declined to undergo SBRT, 10 of whom explicitly preferred cRT. This might be partially explained by more efficient treatment logistics of cRT; in our center; patients who undergo cRT in a single fraction can often be treated on the same day of their visit to the radiation oncologist, or the day after. For the SBRT treatment, there was a waiting time of 1 to 2 weeks because of the use of a vacuum cushion and need for an MRI scan, despite the availability of 2 dedicated MRI scanners for RT purposes at the RT department. This extra waiting time was the reason why many patients to refuse the intervention treatment. In addition, 1 patient had previously been treated for bone metastases with cRT; because he was satisfied with the effect of the previous cRT, he did not want to undergo SBRT. Some differences were seen between the accepters and refusers of SBRT, specifically in primary tumor sites and the use of pain medication. Although this may be due to chance, the higher percentage of lung cancer patients refusing SBRT treatment and more breast cancer patients accepting, could be explained by the differences in prognosis. Patients with breast cancer, who overall have a better prognosis than patients with lung cancer, could be more willing to invest in a more demanding and complex treatment. Furthermore, the percentage of patients not using any pain medication is higher among refusers, whereas their pain scores are similar to those of patients receiving lower levels of analgesia. This finding might indicate that patients had an even higher pain score without the pain medication, and were therefore more likely to accept the more complex experimental treatment.

In addition, 2 patients (4%) who declined SBRT did not want to receive any RT, which was not seen in the cRT arm. Perhaps providing more information to patients in the intervention arm induced hesitation towards the usefulness of both SBRT and cRT.

Our choice to design the VERTICAL study according to TwiCs in order to create real world evidence of the estimated impact of implementing SBRT for pain control in patients with bone metastases, also had some disadvantages. Because of the dropout rate in both arms and the unexpectedly high nonacceptance rate in the SBRT arm, the trial was underpowered to detect the assumed difference in pain response between the cRT and SBRT arms. In addition, in the sample size calculation, an increase of 25% in proportion of patients perceiving a pain response after SBRT compared to cRT was assumed. Therefore, this trial was underpowered to find smaller differences. A substantial pain difference should be present to justify adopting a new treatment, such as SBRT, which poses a considerable higher burden to the patient. Nevertheless, a smaller difference (e.g. 15%) could be considered in further studies.

Despite repeated reminders, the questionnaire return-rates at the different time points ranged from 71% to 78%, and only 39% of the patients returned the questionnaires at all follow-up time points. The relatively low number of returned questionnaires not only reflects the difficulty of conducting studies in vulnerable patient populations; it might also induce a response bias, for example, mainly poor responders fail to return questionnaires. Therefore, the patients who did not return a questionnaire at a given time-point, were considered non-pain-responders in the ITT and PP.

A reason for patients to stop filling out questionnaires were because of increase in disease burden. Other patients indicated they did not find it necessary to complete the questionnaire, because there was no change in their physical situation. Furthermore, the return rate in the control arm was lower than in the intervention arm. This could be because control patients were unaware of being part of a clinical trial.

It has been hypothesized that the duration of response is longer after SBRT because of higher local control [9,30]. Because only 39% of the patients filled out the questionnaires at all follow-up time points, we were unable to make a reliable estimate of the duration of pain response to confirm this suggestion. Furthermore, local control was not assessed in the present study. Future research could include local control as an endpoint, which may be particularly relevant for patient with a relatively high life expectancy. Despite the exclusion criteria of an estimated life expectancy of <3 months, 14 patients died within 3 months after RT. This result shows that the estimation of life expectancy in this patient group is difficult. Multiple prognostic models have been proposed, but so far none is sufficient to make a reliable estimate of the prognosis for all patients. This is a dilemma in all trials conducted with patient with bone metastases.

Finally, we depended on (follow-up) data as collected in the PRESENT cohort. In this cohort, only grade ≥3 adverse events are collected because of the high number of (intervention unrelated) adverse events due to the natural course of disease in patients with stage IV cancer. Furthermore, toxicity was physician-rated, not patient-reported. This might have resulted in an underestimation of toxicity. However, in both RCTs from Nguyen et al. and Sprave et al. no differences were seen in (grade 1 or 2) adverse events after cRT and SBRT [9,10].

Future research to compare the pain response after cRT and SBRT could be considered using the same TwiCs design. Classic RCTs have the disadvantage of slow accrual; this was an issue in the RACOST trial, which was suspended due to the limited patient accrual. The TwiCs design offers higher inclusion rates, but the potential drop-out should be considered in the study design.

Conclusion

This study showed a comparable pain response after cRT or SBRT for painful bone metastases. Furthermore, when given the choice, a substantial proportion of patients preferred to receive cRT over SBRT. In addition, we found a substantial proportion of patients who were unable to complete SBRT treatment, unlike the cRT treatment. Lastly, the use of the TwiCs design is a feasible method to evaluate experimental treatments in the palliative oncology setting.

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Supplementary material

In conducting the systematic review, the following search terms were used:
"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 "tumour" 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

Supplementary table 1. Patient characteristics of patients who accepted or refused the intervention treatment.

	Accepters of SBRT n=33	Refusers of SBRT n=12
Sex — N (%)		
Female	16 (49)	7 (58)
Male	17 (52)	5 (42)
Age — median (IQR)*	67 (63-72)	60 (53-73)
Charlson Comorbidity Index — median (IQR)*†	6 (6-7)	7 (6-8)
Karnofsky Performance Status — median (IQR)*‡	70 (70-80)	80 (55-80)
Primary Tumour —N (%)		
Lung	9 (27)	5 (42)
Breast	8 (24)	1 (8)
Prostate	9 (27)	3 (25)
Other	7 (21)	3 (25)
Location bone metastases — N (%)		
Spine	15 (45)	7 (58)
Non-spine	18 (55)	5 (42)
Pain score (NRS) before radiotherapy —median (IQR)*	7.0 (3-10)	7.5 (5-8)
Pain medication at baseline —N (%) *		
None	4 (12)	3 (25)
Phase 1	12 (36)	3 (25)
Phase 2	1 (3)	0 (0)
Phase 3	16 (49)	6 (50)
Oral morphine equivalent dose —median (IQR)*	60 (40-117)	65 (48-135)
Concomitant systemic treatment	21 (64)	4 (33)
Hormone therapy	10 (30)	1 (8)
Chemotherapy	7 (21)	1 (8)
Targeted therapy	2 (6)	0 (0)
Other	2 (6)	2 (17)

* Abbreviations: IQR: Inter Quartile Range, NRS: Numeric Rating Scale ranging 0 – 10.
†The scale of the Charlson Comorbidity Index ranges from 0 to 40, a higher score indicates a worse prognosis.
‡The Karnofsky Performance-status score is assessed on a 100-point scale, with lower numbers indicating greater disability. Percentages may not add up to 100% due to rounding

Supplementary table 2. Number and proportion of patients reporting a pain response, following the international consensus(n), according to treatment. As proportion of total returned questionnaires. Presented as n/N (%)

	At 2 weeks	At 4 weeks	At 6 weeks	At 8 weeks	At 3 months
cRT					
Pain increase	3 (9%)	4 (12%)	6 (22%)	3 (12%)	4 (17%)
Stable pain	3 (9%)	3 (9%)	6 (22%)	2 (8%)	2 (9%)
Indeterminate	6 (19%)	6 (18%)	2 (7%)	5 (19%)	3 (13%)
Partial response	18 (56%)	15 (45%)	8 (30%)	9 (35%)	9 (39%)
Complete response	2 (6%)	5 (15%)	5 (19%)	7 (27%)	5 (22%)
SBRT					
Pain increase	8 (22%)	11 (31%)	4 (13%)	8 (25%)	4 (13%)
Stable pain	9 (25%)	1 (3%)	4 (13%)	1 (3%)	3 (10%)
Indeterminate	1 (3%)	8 (22%)	4 (13%)	6 (19%)	6 (19%)
Partial response	13 (52%)	11 (31%)	14 (44%)	14 (44%)	14 (45%)
Complete response	5 (20%)	5 (14%)	6 (19%)	3 (9%)	4 (13%)

Supplementary table 3. Linear mixed model analysis of the pain scores at baseline and follow-up.

	Group	BL			week 2			week 4		
		Mean	95% CI	Diff.	Mean[1]	95% CI	Diff.	Mean[1]	95% CI	Diff.
Pain scores	cRT	6.2	5.6-6.8		3.6	2.6-4.6		3.3	2.3-4.3	
	SBRT	6.6	6.0-7.1	0.4	4.0	2.9-5.2	0.4	3.5	2.3-4.7	0.2

Mean scores adjusted for baseline score, primary tumor, treatment arm and the interaction between time and treatment arm.

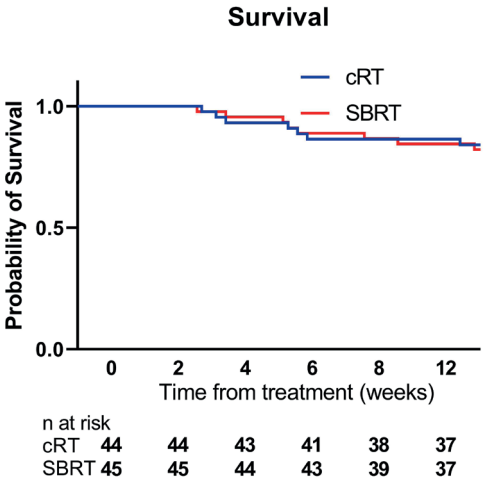
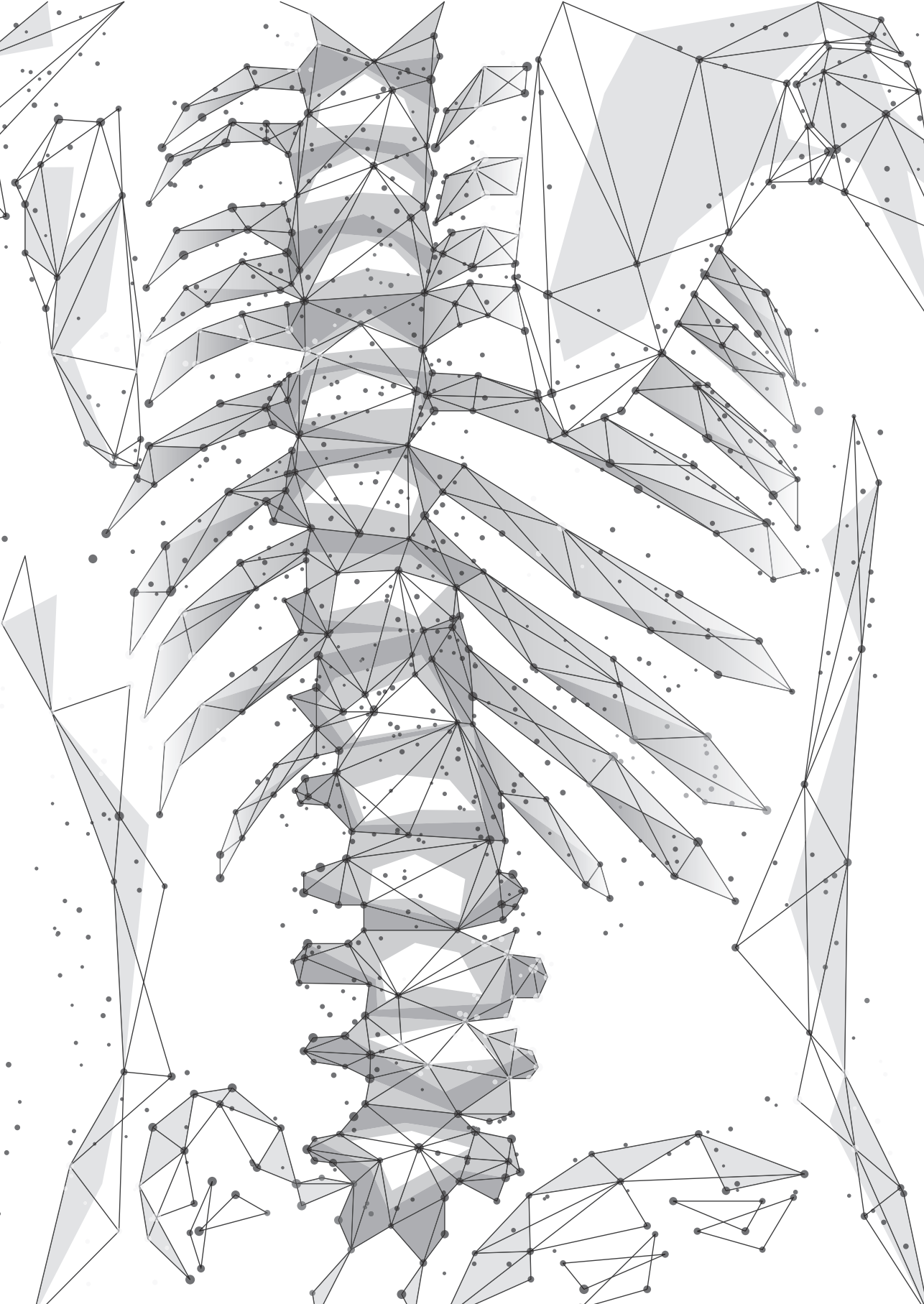


Figure 5. Overall survival after radiotherapy

Supplementary figure 1. Overall survival after RT

week 6			week 8			week 12			p-value[1]
Mean[1]	95% CI	Diff.	Mean[1]	95% CI	Diff.	Mean[1]	95% CI	Diff.	
3.6	2.6-4.6		3.4	2.3-4.4		2.8	1.7-3.9		
2.9	1.7-4.1	-0.7	3.3	2.1-4.5	-0.1	3.5	2.3-4.8	0.7	



CHAPTER 5

Quality of life after stereotactic body radiation therapy versus conventional radiotherapy in patients with bone metastases

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Abstract

Purpose

Painful bone metastases hamper quality of life (QoL). The aim of this prespecified secondary analysis of the VERTICAL trial was to compare change in Global QoL, Physical Functioning, Emotional Functioning, Functional Interference and Psychosocial Aspects after conventional radiotherapy (cRT) versus stereotactic body RT (SBRT).

Material and Methods

A total of 110 patients were enrolled in the phase 2 randomized controlled VERTICAL trial (NCT02364115) following the "Trials within Cohorts" design, randomized 1:1 to cRT or SBRT. Patient-reported Global QoL, Physical Functioning, Emotional Functioning, Functional Interference and Psychosocial Aspects were assessed by the E uropean Organization for Research and Treatment of Cancer QoL Questionnaire (QLQ) Core 15 Palliative Care and QLQ Bone Metastases 22 modules. Changes in QoL domains over time were compared between patients treated with cRT and SBRT using intention-to-treat (ITT) and per protocol (PP) linear mixed model analysis adjusting for baseline scores. Proportions of patients in the cRT versus SBRT arm reporting a clinically relevant change in QoL within 3 months were compared using a chi-square test.

Results

QoL scores had improved over time and were comparable between groups for all domains in both the ITT and PP analyses, except for Functional Interference and Psychological Aspects in the ITT. Functional Interference scores had improved more after 12 weeks in the cRT arm than in the SBRT arm (25.5 versus 14.1 points, respectively, effect size (ES)=0.49, p=0.04). Psychosocial aspects scores had improved more after 8 weeks in the cRT arm than in the SBRT arm (12.2 versus 7.3, ES=0.56, p=0.04) No clinically relevant differences between groups at 12 weeks in terms of Global QoL, Physical Functioning, Emotional Functioning, Functional Interference and Psychosocial Aspects were observed.

Conclusion

Palliative RT improves QoL. Both SBRT and cRT have a comparable effect on patient-reported QoL outcomes in patients with painful bone metastases. Functional Interference and Psychological Aspects scores improved stronger in patients treated with cRT versus patients offered SBRT.

Introduction

Bone metastases are a common manifestation of advanced cancer, causing pain, neurological complaints, (impending) fractures, hypercalcemia and deterioration of overall quality of life (QoL).[1–5] Conventional radiation therapy (cRT), consisting of schedules such as 1 x 8 Gy or 10 x 3 Gy, is the standard local treatment for painful bone metastases. The intent of this palliative intervention is to reduce pain and improve QoL.[3,6] Previous studies have shown that patients with a pain response after radiotherapy experienced a better overall QoL compared to patients without a pain response.[7]

Recently, results from the VERTICAL trial were published, a phase 2 randomized trial, comparing pain response after stereotactic body radiation therapy (SBRT) or cRT in patients with painful bone metastases.[8,9] The rationale behind VERTICAL was that dose escalation using SBRT would lead to improved pain response due to the delivery of a higher (tumoricidal) dose per fraction.[9]

In the primary analysis of the VERTICAL trial, no clinically significant difference in pain response was found between cRT and SBRT, 32% and 40% of the patients respectively.[8] Despite swift pain relief being a very important outcome, other patient reported outcomes (PROs), such as global QoL, Physical Functioning and Emotional Functioning are relevant to patients in the palliative phase of their disease. These outcomes are subjective and multidimensional constructs, and may therefore depend on more factors than pain alone, including limitations in physical and daily functioning, expectations of RT effectiveness at initiation of the treatment, and perception of treatment effectiveness after treatment.[10–12] When expectations are met after RT, patients are more likely to be satisfied with the treatment outcome and may perceive their post-treatment functioning and QoL as more favorable.[13] Such subjective outcomes could be affected by the study design, such as retrospective designs or classics randomized trials where patients know to which arm they are randomized. Among other things, this was the reason that this secondary analysis was performed within the VERTICAL trial, following the Trials within Cohorts (TwiCs) design. So far, only one randomized controlled trial (RCT) evaluated the change in QoL in patients treated with cRT compared with SBRT for painful bone metastases, and this trial did not show superiority of QoL in the SBRT arm as no differences were found between the groups.[10] Here, we present the results of a pre-specified secondary analysis of the VERTICAL trial where we compared the change in various domains of QoL in patients with painful bone metastases treated with cRT compared with those treated with SBRT.

Methods

Study Design

The VERTICAL trial was designed to compare pain response and PROs between patients treated with cRT or SBRT for painful bone metastases (NCT02364115). VERTICAL followed the TwiCs design and was embedded in the PRrospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort.[14,15] In the context of PRESENT, all patients with bone metastases, referred to the radiation oncology department of our tertiary referral hospital are systematically asked to (1) give informed consent for use of their routine clinical data for research purposes, (2) consent to fill out QoL questionnaires and PROs, and (3) provide broad consent for possible future randomization into trials.[16]

Patients

Patients participating in PRESENT who gave broad consent for future randomization and meeting the in- and exclusion criteria for the VERTICAL trial were identified.[9] Inclusion criteria included radiologic and/or histologic evidence of bone metastases, no more than 2 painful lesions requiring radiation treatment, no or mild neurologic signs such as (radiating) pain or numbness, Karnofsky Performance Status scale of 50 points or higher, and pain score of 3 or higher on a numerical rating scale ranging from 0 (no pain) to 10 (worst pain). Exclusion criteria included contraindications to undergo magnetic resonance imaging (MRI); metastasis from a highly radiosensitive tumor (eg, lymphoma); lesions too large for SBRT (ie, >10 cm); estimated life expectancy less than 3 months; previous cRT or SBRT on the same level; need for surgical stabilization; and severe, worsening, or progressive neurologic symptoms. Eligible patients were randomized in a 1:1 ratio to the cRT or SBRT arm using block randomization with alternating block size. After randomization, in line with the TwiCs design, only patients allocated to the SBRT arm were informed about the VERTICAL trial and were offered to undergo SBRT. [16] Informed consent to undergo SBRT was obtained from patients accepting this offer. Patients who refused SBRT were planned for standard treatment (cRT) and remained in the intervention arm for analyses. Patients randomized to the cRT (control) arm were not informed about the VERTICAL trial and received standard cRT. Ethical approval for both the VERTICAL trial and PRESENT was obtained from the Institutional Review Board of the UMC Utrecht, the Netherlands.

Treatment procedures

A detailed protocol for cRT and SBRT planning was published earlier.[9] In the cRT arm, patients received 1 x 8 Gy, 5 x 4 Gy or 10 x 3 Gy. In the SBRT arm, patients received 1 x 18 Gy, 3 x 10 Gy or 5 x 7 Gy.

Data Collection

Within PRESENT, demographic and clinical data were collected prospectively at baseline (before start of RT), at 2, 4, 6 and 8 weeks, 3 and 6 months, and then every six months after treatment until death. Patient comorbidities were summarized using the Charlson Comorbidity Index.[17] Pain scores and PROs were measured in the PRESENT cohort using European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire(QLQ) Core-15 Palliative (C15-PAL) and EORTC-QLQ Bone Metastases 22 (BM22).[11,18,19] In addition, toxicity and adverse events were physician assessed at clinical or telephone follow-up. Adverse events were graded following the CTCAE version 4.0; only adverse events ≥ grade 3 were recorded, because in the study population of patients with stage IV disease, the amount of study-unrelated (low grade) adverse is high. [8]

Outcome measures

The C15-PAL questionnaire consists of 15 questions representing 9 domains: Global QoL, 2 functional scales (Physical Functioning and Emotional Functioning), and 6 symptom scales (Nausea, Loss of Appetite, Dyspnea, Constipation, Sleeping Difficulties and Fatigue).[11] The BM22 questionnaire consists of 22 questions representing four domains: Painful Sites, Pain Characteristic, Functional Interference and Psychosocial Aspects.[18] For both the C15-PAL and BM22 questionnaire, patients rated their response on a 4-point Likert scale. The Global QoL domain was rated using a 7-point Likert scale. Scale scores were linearly transformed to a 0 to 100 scale for the functional and symptom domains.[18] A higher score on the Global QoL and functional scales indicates better QoL and functioning, whereas lower scores on the symptom scales indicate less symptoms.[11] Higher scores on Functional Interference and Psychosocial Aspects domains are more favorable.[18] Patients were considered to have a clinically relevant improvement or deterioration when they had an increase or decrease respectively of 10 points on a 100-points scale compared to the baseline score.[19] For the present study, we focused on Global QoL, Physical and Emotional Functioning of the C15-PAL, and the Functional Interference and Psychosocial Aspects domains of the BM22. Global QoL is a single question domain, depicting the overall QoL. Physical Functioning is a 3-question domain to measure the ability to perform essential physical activities such as self-care. Emotional Functioning is a 2-question domain on patients' feeling of being depressed or tense. Functional Interference is an 8-question domain, measuring the influence of (painful) bone metastases on physical activity, sleep, sitting, and lying down. The Psychosocial Aspects domain is described by 6 questions, measuring hope and worries about the disease, social isolation and social isolation due to the disease. [20]

Statistical analysis

The current study is a predefined secondary analysis of the VERTICAL trial, and no sample-size calculation was performed for the current outcome.[8,9] For the primary analysis, 55 patients had to be included in each treatment arm to find a 25% difference in overall pain response with an α of 5% and a 10% drop-out.

A linear mixed model (LMM) for repeated measurements was used to evaluate the change in QoL scores between the two treatment arms. The scores at follow-up were compared to the baseline scores.

A random intercept for each patient was used to account for between-patients variation, and an autoregressive covariance structure was applied. Missing outcome data was assumed to be as missing at random; the mixed model accounts for such missing data.[21–23] Random slopes did not improve the model and were not included. The models included treatment arm and the interaction between treatment and time as ordinal variable, and the baseline scores, and the interaction between treatment arm and time. The LMM analysis was presented as means for each domain on each time point for both cRT and SBRT, and the mean difference with a 95% confidence interval (95%CI) between the treatment arms. The standardized effect size (ES) was calculated by dividing the mean between group difference at each time point by the pooled standard deviation at baseline.[24] In addition, an ES was calculated for the full model, using the mean difference between the 2 treatment arms without the time as stratification. An ES of ≤0.2 was considered as no difference, 0.2-0.5 was considered a small difference, 0.5-0.8 was considered a moderate difference, and an ES of >0.8 was considered a substantial difference in the reported scores.[25]

Proportions of patients with clinically relevant improvement or deterioration, that is, a change of at least 10 points on a 100-point scale, were compared between the treatment arms at each time point using the χ^2 test.[26] In addition, proportions of patients reporting a clinically relevant improvement at any time point within 12 weeks were compared. Here, patients who did not return a questionnaire were conservatively considered as having no improvement at that time point.

Statistical analyses were performed as intention-to-treat (ITT) and per protocol (PP). In the ITT analysis, all patients were included except for the patients who were not eligible after randomization. In the PP analysis, only patients who completed the treatment according to the random allocation were included. P-values of ≤ .05 were considered statistically significant.

Results

Between January 2015 and March 2019, 110 patients were randomized. After randomization, 11 patients in the cRT arm and 10 patients in the SBRT arm were excluded, as they did not, or no longer, meet the inclusion criteria (Fig. 1). The most common reasons were lack of pain, new need for surgery, or additional MRI showing the lesion to be too large for SBRT. A total of 89 patients were included in the ITT analysis, 44 patients in the cRT arm and 45 in the SBRT arm. The majority of patients were male (n=55, 62%), and the most common primary tumors were lung and prostate (26% and 22%, respectively, Table 1).[8]

Table 1. Baseline characteristics of patients with painful bone metastases enrolled in the VERTICAL trial.

	Conventional Radio-therapy group N=44	Stereotactic Body Radio-therapy group N=45
Sex, no (%)		
Male	31 (70)	24 (53)
Age in years — median (IQR)*	63 (57-73)	65 (61-72)
Charlson Comorbidity Index, median (IQR)*†	6 (6-7)	6 (6-7)
Karnofsky Performance Status, no (%) *‡		
≤50	1 (3)	2 (7)
60-70	11 (37)	14 (40)
80-100	18 (60)	19 (42)
Missing	14 (32)	10 (22)
Primary Tumor Site, no (%)		
Lung	9 (21)	14 (31)
Breast	8 (18)	9 (20)
Prostate	9 (21)	11 (24)
Other	18 (40)	11 (24)
Location bone metastases, no(%)		
Spine	22 (50)	27 (60)
Non-spine	22 (50)	18 (40)
Shoulder	2 (9)	3 (16)
Rib	5 (23)	3 (16)
Pelvis or hip	12 (55)	9 (50)
Other*	3 (14)	3 (16)
Pain score (NRS) at baseline, mean (SD)*	6.2 (2.0)	6.6 (1.8)
Pain medication at baseline, no (%)*		
None	7 (16)	7 (16)
Non-opioid	15 (34)	15 (33)
Strong opioid	22 (50)	23 (51)
Oral morphine equivalent dose, median (IQR)	60 (40-120)	60 (40-110)
Concomitant systemic treatment*	17 (39)	25 (56)
Hormone therapy	7 (16)	11 (24)
Chemotherapy	7 (16)	10 (22)
Targeted therapy	2 (4)	2 (4)
Other	1 (2)	2 (4)

Abbreviations: IQR: Inter Quartile Range, NRS: Numeric Rating Scale ranging 0 – 10. †The scale of the Charlson Comorbidity Index ranges from 0 to 40, a higher score indicates a worse prognosis. Patients with bone metastases have a score of at least 6. ‡The Karnofsky Performance-status score is assessed on a 100-point scale, with lower numbers indicating greater disability. *cRT arm: kidney (n=5), Bladder (n=4), colon and rectum (n=5), oesophagus (n=1), another endocrine (n=1). SBRT arm: bladder (n=4), kidney (n=3), colon and rectum (n=1), stomach (n=1), oesophagus (n=1), another upper digestive tract (n=1) Percentages may not add up to 100% due to rounding

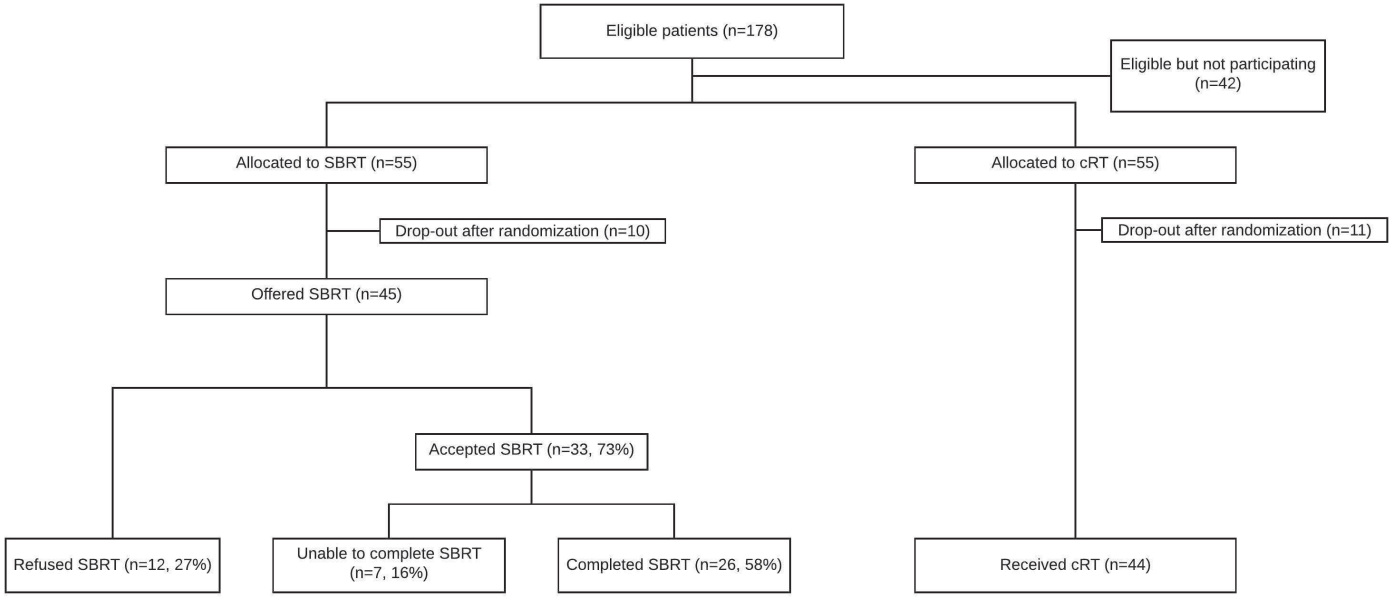

Figure 1. Flowchart of patient enrolled in the VERTICAL trial and treatment allocation.

After randomization, 12 of the 45 patients (27%) who were offered SBRT refused and chose to undergo cRT or no treatment (Fig. 1). The major reason to not undergo SBRT was the longer waiting time for treatment compared with cRT. Furthermore, 7 patients (16%) were unable to fully undergo SBRT due to various reasons, for example, increase in pain after 1 SBRT fraction or rapid deterioration between fractions. Subsequently, all 44 patients in the cRT and 26 patients in the SBRT arm were analyzed in the PP analysis. In the cRT arm, 21 patients (48%) received 1 x 8 Gy, 6 patients (14%) received 5 x 4 Gy and 17 patients (39%) received 10x3 G. In the SBRT arm, 6 patients (23%) received 1 x 18 Gy, 11 patients (42%) received 3 x 10 Gy and 9 patients (35%) received 5 x 7 Gy.

The proportion of patients returning a questionnaire varied over time from 49% in week 12 to 78% at baseline (Supplementary table 1). The return rate in the cRT arm was not statistically different at any follow-up time point compared with the SBRT arm (p=0.81 at baseline, p=0.06 at 12 weeks, Supplementary table 1). During the reminder telephone calls, patients indicated that they did not return their questionnaires for a variety of reasons: some indicated a lack of energy to fill out the questionnaires as a result of disease progression, whereas others reported that the treatment had a positive effect, and they therefore no longer saw a reason to return the questionnaires.

In the LMM analysis, no interaction was found between treatment and time and each separate follow-up point. Therefore, an overall score ES was calculated as well, to compare the course of the QoL scores between the treatment arms (Tables 2 and 3). Compared to baseline scores, a positive change in QoL scores at some point during the 12 weeks after treatment was observed in all domains in both the ITT and PP analyses, specifically in the Psychosocial Aspects and Functional Interference domains (Table 2 and 3, Figs. 2 and 3). Figures 2 and 3 show a difference in course of QoL scores between the treatment arms. However, these visible differences did not translate into significant overall differences in the LMM analyses for the course of the QoL scores.

In the ITT LMM analysis, there was a significant difference at 12 weeks of 10.6 points (95% CI -21.0 to -0.3; ES = 0.62) between the cRT and the SBRT arm in Functional Interference in favor of cRT (Table 2). Between baseline and 12 weeks after treatment, Functional Interference scores improved from 55.0 (95%CI 49.6-64.1) to 80.5 (95% CI 72.8-88.2) and from 55.8 (95%CI 48.7-62.9) to 69.9 (95% CI 63.2-76.5) in respectively the cRT and SBRT arm (Table 2). There was a comparable, but nonsignificant, course of Function Interference scores. In the PP LMM analysis, no significant differences were found between the treatment arms.

Table 2 Linear mixed model intention-to-treat analysis for all QoL domains of the EORTC QLQ-C15 and BM22 questionnaires, comparing QoL between patients treated with cRT or SBRT

Domain	Group	Baseline	Week 4				Week 8				Week 12				During 12 weeks
		Mean	Mean†	MD*	95% CI*	ES	Mean†	MD*	95% CI*	ES	Mean†	MD*	95% CI*	ES	ES
C15															
Global QoL	cRT	57.8	64.3				68.1				65.2				
	SBRT	59.8	60.8	-3.5	-15.9 to 8.9	0.18	63.6	-4.4	-16.9 to 8.1	0.23	65.5	0.2	-12.4 to 12.9	0.01	0.13
Physical Functioning	cRT	58.6	63.8				63.1				67.5				
	SBRT	62.4	59.6	-4.2	-15.5 to 7.2	0.16	59.3	-3.8	-17.1 to 9.4	0.15	60.4	-7.2	-18.8 to 4.5	0.28	0.19
Emotional Functioning	cRT	73.8	73.2				86.4				80.7				
	SBRT	63.7	77.4	4.2	-8.5 to 16.9	0.19	75.3	-11.1	-24.0 to 1.8	0.50	73.6	-7.2	-20.0 to 5.8	0.32	0.22
BM22															
Functional Interference	cRT	55.0	67.6				75.2				80.7				
	SBRT	58.3	65.0	-2.6	-13.0 to 7.9	0.12	69.0	-5.2	-15.6 to 5.2	0.26	72.9	-7.9	-18.6 to 2.8	0.39	0.22
Psychosocial Aspects	cRT	55.4	56.6				58.1				56.1				
	SBRT	49.2	55.4	-1.1	-9.5 to 7.3	0.06	58.5	0.4	-8.1 to 8.9	0.02‡	59.7	3.6	-4.9 to 12.2	0.20	0.05‡

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; CI = confidence interval; cRT = conventional
radiation therapy; ES = effect size; MD = mean difference; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.
* Mean scores for the QoL domains of the EORTC QLC-C15 Palliative Care (EORTC QLQ-C15-PAL) and EORTC QLQ-BM22. Scores range from 0 to 100. Higher scores indicate better QoL.
† Mean difference in scores between the cRT arm and SBRT arm with 95% CI.
* Statistically significant difference between cRT and SBRT. A P value <0.05 is considered statistically significant. The effect size represents the difference between the cRT-arm and SBRT-arm in QoL scores

Table 3. Linear mixed model per-protocol analysis for all QoL domains of the EORTC QLQ-C15 and BM22 questionnaires, comparing QoL between patients treated with cRT or SBRT.

Domain	Group	Baseline	Week 4				Week 8				Week 12				During 12 weeks
		Mean	Mean†	MD*	95% CI*	ES	Mean†	MD*	95% CI*	ES	Mean†	MD*	95% CI*	ES	ES
C15															
Global QoL	cRT	57.8	64.3				68.1				65.2				
	SBRT	59.8	60.8	-3.5	-15.9 to 8.9	0.18	63.6	-4.4	-16.9 to 8.1	0.23	65.5	0.2	-12.4 to 12.9	0.01	0.13
Physical Functioning	cRT	58.6	63.8				63.1				67.5				
	SBRT	62.4	59.6	-4.2	-15.5 to 7.2	0.16	59.3	-3.8	-17.1 to 9.4	0.15	60.4	-7.2	-18.8 to 4.5	0.28	0.19
Emotional Functioning	cRT	73.8	73.2				86.4				80.7				
	SBRT	63.7	77.4	4.2	-8.5 to 16.9	0.19	75.3	-11.1	-24.0 to 1.8	0.50	73.6	-7.2	-20.0 to 5.8	0.32	0.22
BM22															
Functional Interference	cRT	55.0	67.6				75.2				80.7				
	SBRT	58.3	65.0	-2.6	-13.0 to 7.9	0.12	69.0	-5.2	-15.6 to 5.2	0.26	72.9	-7.9	-18.6 to 2.8	0.39	0.22
Psychosocial Aspects	cRT	55.4	56.6				58.1				56.1				
	SBRT	49.2	55.4	-1.1	-9.5 to 7.3	0.06	58.5	0.4	-8.1 to 8.9	0.02‡	59.7	3.6	-4.9 to 12.2	0.20	0.05‡

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; CI = confidence interval; cRT = conventional
radiation therapy; ES = effect size; MD = mean difference; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.
* Mean scores for the QoL domains of the EORTC QLC-C15 Palliative Care (EORTC QLQ-C15-PAL) and EORTC QLQ-BM22. Scores range from 0 to 100. Higher scores indicate better QoL.
† Mean difference in scores between the cRT arm and SBRT arm with 95% CI.
* Statistically significant difference between cRT and SBRT. A P value <0.05 is considered statistically significant. The effect size represents the difference between the cRT-arm and SBRT-arm in QoL scores

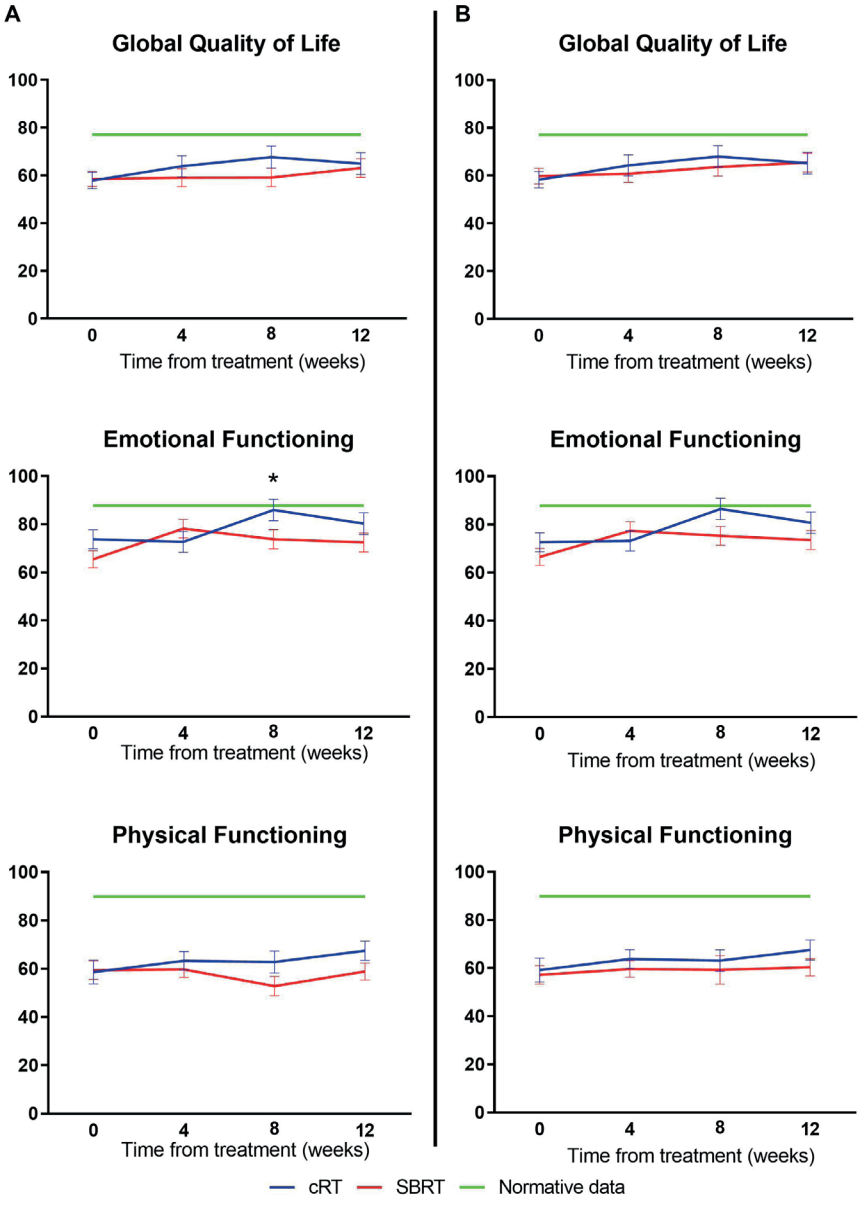

Figure 2. Quality of life domains of the C15-PAL questionnaires in the ITT mixed model analysis. (A) In the ITT analysis, all patients were included except for the patients who we found not eligible after randomization. (B) In the PP analysis, only patients who completed the treatment according to the random allocation were included. A higher score depicts an improved quality of life. Normative data show the mean score of the general, cancer-free population. *Significant difference. Abbreviations: C15-PAL = Quality of Life Questionnaire Core 15 Palliative Care; ITT = intention to treat; PP = per protocol.

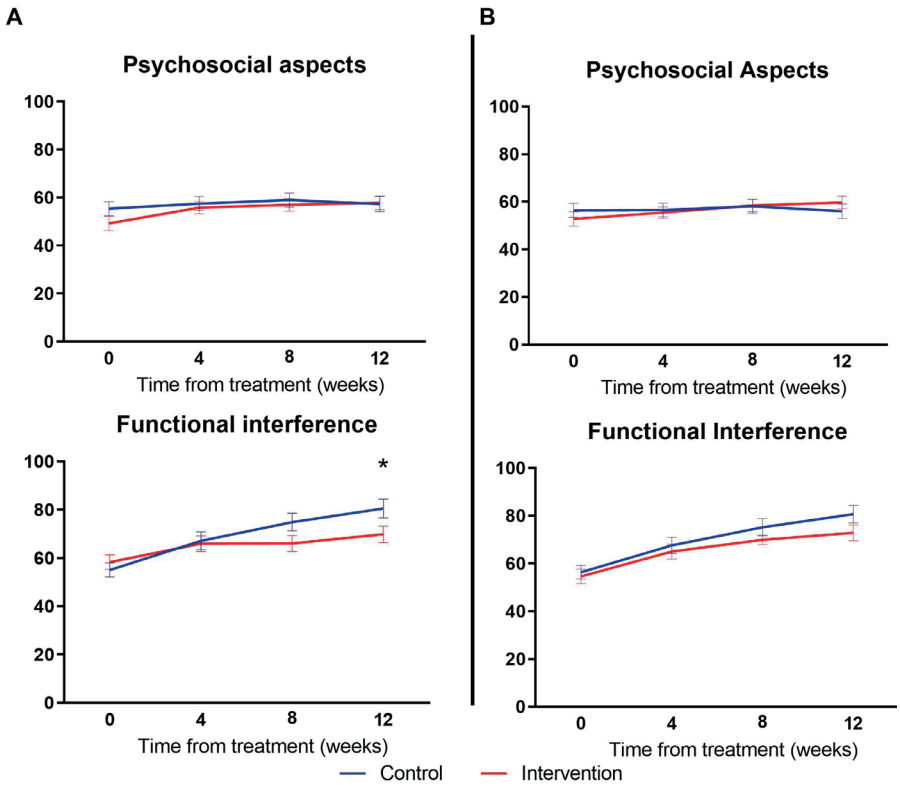

Figure 3. Quality of life domains of the BM22 questionnaires in the ITT mixed model analysis. (A) In the ITT analysis, all patients were included except for the patients who we found not eligible after randomization. (B) In the PP analysis, only patients who completed the treatment according to the random allocation were included. A higher score depicts an improved quality of life. *Significant difference. Abbreviations: BM22 = QLQ Bone Metastases 22; ITT = intention to treat; PP = per protocol.

In the ITT analysis, a (small) majority of patients in both arms reported a clinically relevant improvement in the Global QoL (55% and 56% in the cRT and SBRT arm, respectively) and Emotional Functioning (55% and 64% in the cRT and SBRT arm, respectively) domains at 1 or more time points within 12 weeks after treatment (Table 2 and 3). Nevertheless, the proportion of patients with a clinically relevant improvement was not significantly different between treatment arms within 12 weeks after RT (Tables 4 and 5). In the PP analysis, the proportion of patients with a clinically significant difference in the cRT arm remained unchanged compared to the ITT analysis (Tables 4 and 5). However, in the SBRT arm, a higher proportion of patients had clinically significant improvement for several domains (tables 4 and 5). However, differences in proportions of patients with a clinically relevant difference between the cRT and SBRT arms were not statistically significant in the PP analysis either.

Table 4 Number of patients in the intention-to-treat analysis reporting a clinically relevant improvement in selected QoL domains of the EORTC QLQ-C15 and BM22 questionnaires

	Group					
		Week 4	**Week 8**	**Week 12**	**Within 12 weeks**	***P* value ***
Cumulative deaths	cRT	1	5	7	7	
	SBRT	0	6	7	7	
Domains						
C15		n/N (%)‡	n/N (%)‡	n/N (%)‡	n/N (%)‡	
Global QoL	cRT	16/43(37)	17/39 (44)	17/37 (46)	24/44 (55)	
	SBRT	19/45 (42)	17/39 (38)	21/38 (55)	25/45 (56)	0.12
Physical Functioning	cRT	16/43 (37)	7/39 (18)	7/37 (19)	18/44 (41)	
	SBRT	16/45 (36)	6/39 (13)	10/38 (26)	20/45 (44)	0.83
Emotional functioning	cRT	15/43 (35)	19/39 (49)	13/37 (35)	24/44 (55)	
	SBRT	23/45 (51)	18/39 (40)	17/38 (44)	29/45 (64)	0.52
BM22						
Functioning Interference	cRT	3/43 (7)	3/39 (7)	2/37 (5)	4/44 (9)	
	SBRT	4/45 (9)	3/39 (7)	0/38 (0)	5/45 (11)	1.00
Psychosocial Aspects	cRT	4/43 (9)	2/39 (5)	4/37 (11)	8/44 (18)	
	SBRT	7/45 (16)	3/39 (7)	3/38 (8)	9/45 (20)	1.00

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; cRT = conventional radiation therapy; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* P value is based on the difference of the proportion of patients with a clinically significant response between cRT and SBRT within 12 weeks after RT.

‡ Number of patients with a clinically relevant increase (n), defined as an increase of at least 10 points on a 100-point scale, compared with baseline score among the total number of patients alive at each point in follow-up (N) in the intention-to-treat analysis

Table 5 Number of patients in the per-protocol analysis reporting a clinically relevant improvement in selected QoL domains of the EORTC QLQ-C15 and BM22 questionnaires

	Group	Week 4	Week 8	Week 12	Within 12 weeks	*P* value *
Cumulative deaths	cRT	1	5	7	7	
	SBRT	0	6	7	7	
Domains						
C15		n/N (%)‡	n/N (%)‡	n/N (%)‡	n/N (%)‡	
Global QoL	cRT	16/43(37)	17/39 (44)	17/37 (46)	24/44 (55)	
	SBRT	19/45 (42)	17/39 (38)	21/38 (55)	25/45 (56)	0.12
Physical Functioning	cRT	16/43 (37)	7/39 (18)	7/37 (19)	18/44 (41)	
	SBRT	16/45 (36)	6/39 (13)	10/38 (26)	20/45 (44)	0.83
Emotional functioning	cRT	15/43 (35)	19/39 (49)	13/37 (35)	24/44 (55)	
	SBRT	23/45 (51)	18/39 (40)	17/38 (44)	29/45 (64)	0.52
BM22						
Functioning Interference	cRT	3/43 (7)	3/39 (7)	2/37 (5)	4/44 (9)	
	SBRT	4/45 (9)	3/39 (7)	0/38 (0)	5/45 (11)	1.00
Psychosocial Aspects	cRT	4/43 (9)	2/39 (5)	4/37 (11)	8/44 (18)	
	SBRT	7/45 (16)	3/39 (7)	3/38 (8)	9/45 (20)	1.00

Abbreviations: BM22 = European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) Questionnaire (QLQ) Bone Metastases 22; cRT = conventional radiation therapy; QLC-C15 = EORTC QLC Core 15; SBRT = stereotactic body radiation therapy.

* P value is based on the difference of the proportion of patients with a clinically significant response between cRT and SBRT within 12 weeks after RT.

‡ Number of patients with a clinically relevant increase (n), defined as an increase of at least 10 points on a 100-point scale, compared with baseline score among the total number of patients alive at each point in follow-up (N) in the intention-to-treat analysis

In both the ITT and PP analyses, a minority of the patients had a clinically relevant deterioration in QoL domains in each arm (Supplementary table 2). In the PP analysis, the difference in proportion of patients with a clinically relevant improvement between the 2 groups changed in favor of the SBRT arm but remained nonsignificant. The proportion of patients with clinically relevant deterioration were comparable between the 2 treatment arms. As reported previously in the primary analysis, no treatment-related Criteria for Adverse Events grade 3 or 4 adverse events within 3 months after treatment were reported in either treatment arm.[8]

Discussion

Our study shows that there was no difference in change in QoL between treatment with cRT or SBRT for painful bone metastases. Nonetheless, QoL improved in the majority of patients at some point in the 3 months following treatment. Patients receiving cRT reported larger improvements in terms of Functional Interference of pain with daily functioning and Psychosocial Aspects compared to patients receiving SBRT. The absence of superior QoL scores among patients in the SBRT arm was not unexpected. The primary analysis of the VERTICAL trial showed no differences between the cRT and SBRT in terms of pain response (32% and 40% of the patients respectively). As pain is considered to be one of the main elements in QoL, we also did not expect a significant difference in QoL between the cRT arm and SBRT arm.[8,27]

Our results are in line with the results of the secondary analysis of Sprave et al.[10] In their exploratory trial comparing SBRT and cRT, 55 patients were randomized to either 1 x 24 Gy SBRT, or 10 x 3 Gy cRT. In their study, QoL was measured using the EORTC-QLQ BM22 and EORTC-QLQ FA13 (fatigue) questionnaires directly after RT, and 3 and 6 months after RT. They showed an improvement in all QoL domains but no significant difference between the cRT and the SBRT arm. To our knowledge, the trial performed by Sprave et al. is the only trial directly comparing QoL between cRT and SBRT in patients with bone metastases albeit with a somewhat protracted 10 fractions cRT schedule.[28] In addition to the QoL domains, a secondary analysis was performed on bone mineral density and vertebral compression fractures (VCF).[29] In this secondary analysis, Sprave et al. found an increase of VCF in patients treated with SBRT compared to cRT. This could influence the pain and QoL response in patients treated with SBRT with a VCF. Other trials have reported the results of cRT versus SBRT on pain response, but no results on the QoL have yet been published. [30–32] Furthermore, the ROBOMET Trial (A Trial to Improve Quality of Life With Stereotactic Body Radiotherapy for Patients With Painful Bone Metastases; clinical trial NCT03831243; recruiting until 2023) and the PREST trial (Reduction of Pain Symptoms With Stereotactic Radiotherapy on Bone Metastases; clinical trial NCT03597984; awaiting commencement) aim to compare QoL between cRT and SBRT in patients with painful bone metastases. [33,34]

Because to drop-out after randomization, both ITT and PP analyses were performed. In the ITT analysis, all patients who were found ineligible after randomization were excluded. For the PP analysis, only patients who completed the allocated treatment were included, leaving out another 19 SBRT patients. We found more often a clinically relevant improvement after SBRT in the PP analyses. In these analyses, the patients willing to wait and able to undergo the entire SBRT treatment remained, and it is likely that these patients were in a better clinical condition than the patients

dropping out. As a result of the selection due to drop-out after randomization, patients included in the PP were presumably in a better general condition than the patients who could not complete the treatment (Supplementary table 3). It could be expected that this selection could change the outcome of the analysis in favor of the SBRT arm in which the selection took place. Nonetheless, in the PP analysis, no major significant differences between the groups were found.

Although most QoL domains showed a comparable trend for both the cRT and SBRT arms, there was a significant difference between the cRT and SBRT arm in the change in Functional Interference scores at 12 weeks in favor of the cRT arm. Functional interference of pain with daily functioning reflects a patient's ability to do lie down, sit and do moderate activities. Although SBRT needs more preparatory time including additional MRI, stabilization in vacuum mattress, more treatment time on linear particle accelerators, this probably does not reflect in Functional Interference domain in short-term. The time to observe an effect of SBRT might be delayed which might explain that we only see a difference at 12 weeks follow-up.

The VERTICAL study is the first trial following the TwiCs design in the palliative setting. Previous studies following the TwiCs design showed that the representativeness of patients is higher in trials using the TwiCs design compared to a classic RCT.[35,36] For the VERTICAL trial, patients participating in the PRESENT cohort who were eligible to undergo SBRT were selected and randomized without any additional selection. In the PRESENT cohort, all patients are asked to participate in the cohort, and if they wanted to participate in future studies on experimental interventions.[8] Therefore, the results of the VERTICAL trial are more generalizable to the real-world population of patients eligible for treatment with SBRT for painful bone metastases compared with patients in classic RCTs comparing SBRT and cRT.[37,38] However, this is negatively influenced by the drop-out after randomization in this trial.

Another advantage of the TwiCs design is that it may prevent disappointment bias by not informing (and potentially disappointing) patients allocated to the control arm. In a classic RCT, patient are informed about an innovative treatment that could induce hope for better results. Due to the knowledge of being allocated to the control arm, patients could rate their outcomes more negatively.[39] Therefore, the TwiCs design could be especially relevant in trials with subjective outcomes such as pain and QoL. The opposite, however, may have happened as well: patients in VERTICAL, who were offered SBRT, may have had overly optimistic expectations.[12] When the high expectations were not met, disappointment could have been reflected in the self-reported QoL scores. In the cRT arm, where patients were not informed about the trial, the impact of this disappointment bias was limited or non-existent.[39] This could influence the QoL-scores positively in the cRT and negatively in the SBRT arm. This negative influence on the outcomes in the SBRT

arm, could be reinforced by the increased burden of the treatment. Nonetheless, as pain and QoL are subjective scores, they could also be positively influenced by the idea of receiving a new and innovative treatment.

The VERTICAL trial was primarily powered to detect a difference in pain response. Because of the unexpected high number of patients in the intervention arm refusing to undergo SBRT, and the high number of patients unable to complete SBRT, the primary analysis was underpowered to detect a difference in pain. As such, the current study was not powered to detect clinically relevant differences in the QoL domains. Nonetheless, proportions of patients with a clinically relevant improvement did not differ between the 2 groups. Because of the drop-out after randomization, a PP analysis was performed in addition to the ITT to examine the true effect of SBRT versus cRT. Owing to the additional analysis, and thus the induced multiple comparison, an additional study could be performed with an increased number of patients to adjust for the drop-out.

In addition, the number of returned questionnaires in both arms was less than expected, despite follow up calls to remind patients, which could have influenced the results. For some patients their disease progressed over time, leaving them unable to return questionnaires. Other patients informed the researcher the pain from the metastases and QoL improved and therefore they stopped filling out the questionnaires. Notably, and probably due to the design, the proportion of patient returning questionnaires was lower in the cRT arm. The awareness of being part of a clinical trial —more often the case for patients in the SBRT arm— might have positively affected the return rate of questionnaires. In the figures, a difference is seen in the trend of the QoL scores between the treatment arms. Nonetheless, this difference is limited in the LMM analysis. The difference could be too small to be detected in this trial due to the drop-out and limited return of questionnaires.

Lastly, this study only evaluated PROs in the first 12 weeks following RT, while the duration of the effect of RT might differ between cRT and SBRT, where the effect of SBRT could last longer. [10] Therefore, future studies should study the effects on the longer term as well.

Conclusion

In this secondary analysis of the VERTICAL trial, we found that both cRT and SBRT had a comparable positive effect on all QoL domains in patients irradiated for painful bone metastases. Improvement in functional interference and psychological aspects was slightly greater in the cRT arm.

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Supplementary files

Supplementary Table 1. Number of patients that returned questionnaires at each follow-up moment**.**

	Baseline	p-value†	Week 4	p-value†	Week 8	p-value†	Week 12	p-value†
cRT	34/44 (77)		24/43 (56)		22/39 (56)		18/37 (49)	
SBRT	35/45 (78)	0.81	28/45 (62)	0.61	27/39 (69)	0.27	26/38 (68)	0.06

Presented as n/N (%); number of patients that returned questionnaires (n) of total patients at each follow-up moment (N).
Abbreviations: cRT, conventional radiotherapy; SBRT, stereotactic body radiation therapy.
†P-value is based on the difference of the proportion of patients returning the questionnaire using a chi-square test.

Supplementary table 2. Number of patients reporting a clinically relevant deterioration in selected QoL domains of the EORTC-QLQ-C15 and BM22 questionnaires at the last filled-out questionnaire within 12 weeks after treatment.

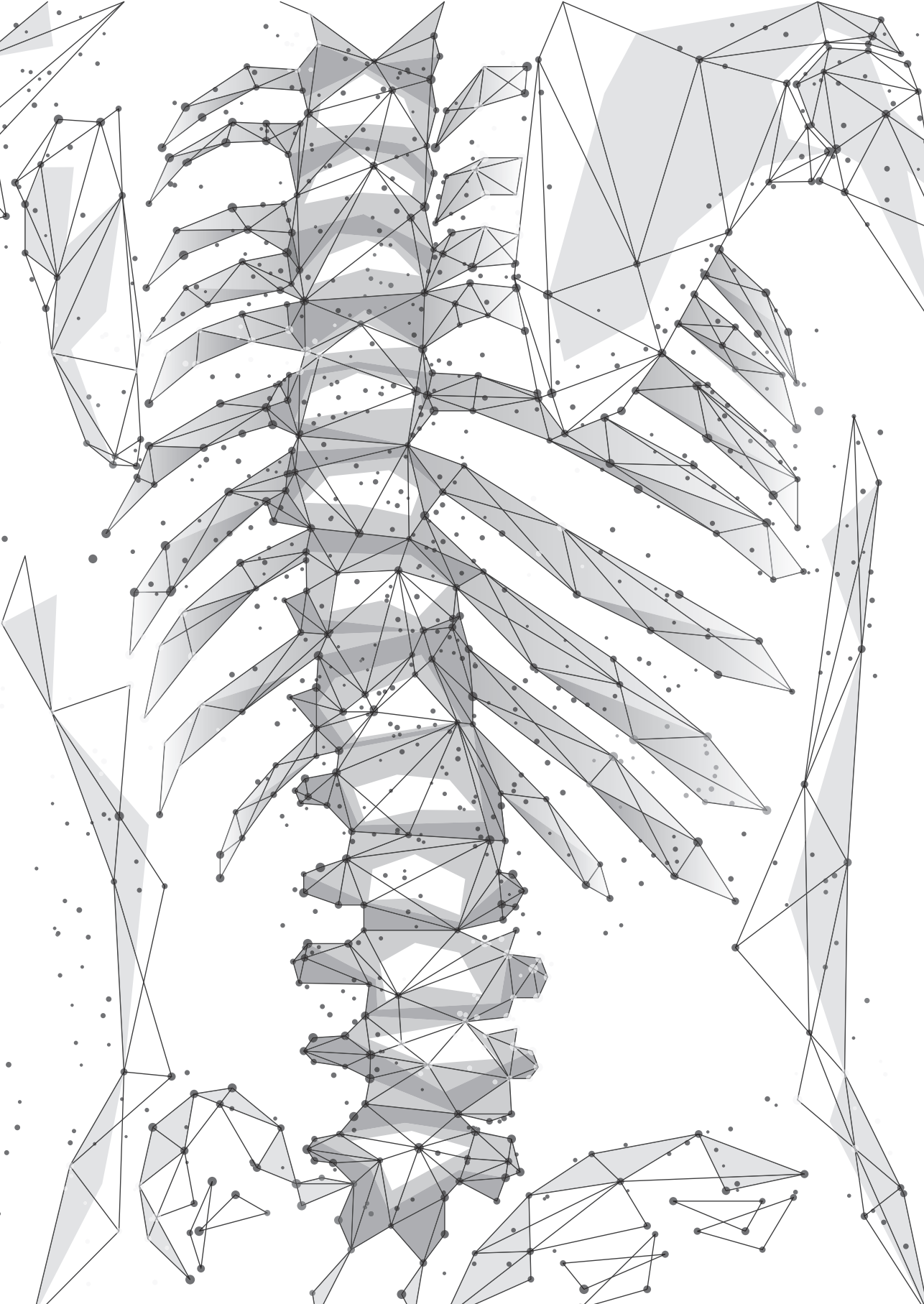
	Group				
		ITT-analysis	p-value†	PP analysis	p-value†
Domains					
C15		n/N (%)‡		n/N (%)‡	
Global QoL	**cRT**	4/44 (9)		4/44 (9)	
	SBRT	8/45 (18)	0.52	5/26 (19)	0.49
Physical Functioning	**cRT**	7/44 (16)		7/44 (16)	
	SBRT	10/45 (22)	0.77	6/26 (23)	1.00
Emotional Functioning	**cRT**	3/44 (7)		3/44 (7)	
	SBRT	8/45 (18)	0.20	5/26 (19)	0.44
BM22					
Functioning Interference	**cRT**	13/44 (36)		16/44 (36)	
	SBRT	14/45 (31)	0.19	11/26 (42)	0.55
Psychosocial Aspects	**cRT**	8/44 (18)		8/44 (18)	
	SBRT	11/45 (24)	0.78	10/26 (38)	0.24

† P-value is based on the difference of the proportion of patients with a clinically significant response between cRT and SBRT within 12 weeks after RT.
‡ Number of patients with a clinically relevant increase (n), defined as an increase of at least 10 points on a 100-point scale compared to baseline score, among the total number of patients alive at each point in follow-up (N) in the intention-to-treat analysis.
Abbreviations: BM22, QLQ-BM22 questionnaire; C15, QLQ-C15-PAL questionnaire; cRT, conventional radiotherapy; ITT, intention-to-treat; PP, Per Protocol; QoL, quality of life; SBRT, stereotactic body radiation therapy

Supplementary table 3. Patient characteristics of patients who accepted or refused the intervention treatment.

	Accepters of SBRT n=33	Refusers of SBRT n=12
Sex — N (%)		
Female	16 (49)	7 (58)
Male	17 (52)	5 (42)
Age — median (IQR)	67 (63-72)	60 (53-73)
Charlson Comorbidity Index — median (IQR)†	6 (6-7)	7 (6-8)
Karnofsky Performance Status — median (IQR)‡	70 (70-80)	80 (55-80)
Primary Tumour —N (%)		
Lung	9 (27)	5 (42)
Breast	8 (24)	1 (8)
Prostate	9 (27)	3 (25)
Other	7 (21)	3 (25)
Location bone metastases — N (%)		
Spine	15 (45)	7 (58)
Non-spine	18 (55)	5 (42)
Pain score (NRS) before radiotherapy —median (IQR)*	7.0 (3-10)	7.5 (5-8)
Pain medication at baseline —N (%)		
None	4 (12)	3 (25)
Phase 1	12 (36)	3 (25)
Phase 2	1 (3)	0 (0)
Phase 3	16 (49)	6 (50)
Oral morphine equivalent dose —median (IQR)	60 (40-117)	65 (48-135)
Concomitant systemic treatment	21 (64)	4 (33)
Hormone therapy	10 (30)	1 (8)
Chemotherapy	7 (21)	1 (8)
Targeted therapy	2 (6)	0 (0)
Other	2 (6)	2 (17)

† The scale of the Charlson Comorbidity Index ranges from 0 to 40, a higher score indicates a worse prognosis.
‡ The Karnofsky Performance-status score is assessed on a 100-point scale, with lower numbers indicating greater disability. Percentages may not add up to 100% due to rounding.
Abbreviations: IQR, Inter Quartile Range; NRS, Numeric Rating Scale ranging 0 – 10



CHAPTER 6

Remineralization of lytic spinal metastases after radiotherapy

Submitted

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Abstract

Purpose

Palliative radiotherapy (RT) can lead to remineralization of osteolytic lesions thereby potentially restoring some of the weight-bearing capacity and preventing vertebral collapse. It is not clear, however, under which circumstances remineralization of osteolytic lesions occurs. The aim of this study was to investigate the change in bone mineral density in spinal metastases after RT compared to a reference region, and find associated factors.

Methods

Patients with spinal metastases were included if computed tomography scans both pre- and post-RT were available. Bone density was measured in Hounsfield units (HU). A region of interest (ROI) was drawn manually in the metastatic lesion. As a reference, a measurement of bone density in adjacent, unaffected, and non-irradiated vertebrae was used. Factors tested for association were origin of the primary tumor, RT dose and fractionation scheme, and concomitant use of bisphosphonates.

Results

A total of 31 patients with 49 spinal metastases, originating from various primary tumors, were included. The median age on baseline was 58 years (IQR: 53–63) and median follow up was 0.68 years (IQR: 0.25–1.53). Difference in HU in the lesion before and after treatment was 146.9 HU (95% CI 68.4–225.4; $p<.01$). Difference in HU in the reference vertebra between baseline and first follow-up was 19.1 HU (95% CI -47.9–86.0; $p=.58$). Difference between reference vertebrae and metastatic lesions on baseline was -194.1 HU (95% CI -276.2– -112.0; $p<.01$). After RT, this difference was reduced to -50.3 HU (95% CI -199.6–99.0; $p=.52$). Patients using bisphosphonates showed a greater increase in HU, 194.1 HU versus 60.6 HU, $p=.01$.

Conclusion

Palliative radiation of osteolytic lytic spinal metastases is positively associated with an increased bone mineral density at follow-up. The use of bisphosphonates was linked to an increased bone mineral density when used during or after RT.

Introduction

The spine is the most commonly affected site in patients with metastatic bone disease (1). Locally secreted tumor cell factors increase osteoclast activity, thereby adversely affecting the bony architecture of the vertebrae, which leads to a decrease in bone mineral density (BMD). Continued weakening of the osseous structures can lead to instability due to increased stress and subsequent failure of the vertebra (2,3). Pathologic fractures often cause severe pain and may lead to neurological impairment.

Treatment of (spinal) bone metastases aims at improving the patient's quality of life by reducing pain and preserving or improving the patient's neurological function (4,5). Unstable spinal metastases often need surgical stabilization (6–8). Although effective spinal surgery is subject to risks of serious complications and adverse events (6,9). Nevertheless, surgery usually resolves spinal instability. If there is no gross mechanical instability and/or neurological impairment, surgical stabilization is not essential and treatment of symptomatic spinal metastases can be performed using radiotherapy (RT) to achieve local tumor control and reduce pain. (6,8,10,11).

When local tumor control is achieved after RT, the balance between osteoblast and osteoclast activity may be restored since these cells, responsible for bone turnover, no longer respond to the negative influences of tumor cytokines (12). Osteoclast activity is triggered after RT and therefore the osteoclast inhibiting property of bisphosphonates (if administered) is considered to attribute to an additional remineralization effect following RT (13,14). The restored balance between osteoblast and osteoclast activity, together with improved patient mobility and subsequent increase in axial loading, may promote bone growth and partially restore bone architecture (3,15). The improved bone architecture and new bone depositions are associated with elevated BMD, measurable on imaging. The improved bone architecture and higher BMD are also associated with an increased weight-bearing capacity of vertebrae (12,16–18). However, little is known about how treatment and disease-related factors influence the extent of restoration of bone strength that may be achieved with RT. Understanding and quantifying the remineralization process after RT can help to tailor the radiotherapeutic dose and scheme. It can further help to retain ideal patient circumstances for remineralization and improving mechanical stability. This could potentially reduce the need for surgical stabilization (2,18). BMD could be measured using Hounsfield Units (HU), a standardized linear coefficient representing the X-ray attenuation. HU values for bone range from -300 to 2000 and air has an HU of -1000. Higher HU reflect an increased BMD (19). The study by *Patel et al.* showed mean HU for vertebrae of 195.7 (95% CI 171.4–220.0) in non-osteoporotic bone (20).

The primary aim of this retrospective analysis was to quantitatively evaluate the phenomenon of remineralization of osteolytic spinal metastases following RT, and compare the change in BMD in the lytic lesion to a reference vertebra outside of the irradiation field. The secondary aim was to determine a possible association between disease and treatment-related factors and the remineralization effect.

Methods

Patient selection and data collection

For this retrospective study, patients were collected from the PRospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort. (21) All patients treated with radiotherapy for bone metastases were systematically invited to participate in the PRESENT cohort. Patients were asked for informed consent to prospectively collect baseline demographics, treatment characteristics, and clinical follow-up data. For the current analysis, data of patients included in the period of June 2013 until January 2018 were used.

Inclusion criteria were palliative RT for at least one osteolytic spinal lesion. The classification of a lesion being osteolytic was based on the description of the lesion in the patient records and was re-assessed on CT data before inclusion. Metastases were considered osteolytic when an evident region of bony destruction/disappearance, and therefore a visible decrease in HU, was observed within a vertebra on CT imaging. For a reliable measurement, the lesion had to be larger than the predefined region of interest (ROI [5mm]). Furthermore, patients could only be included if they had at least one follow-up CT scan available between treatment and the end-of-study period. Patients were excluded when they had surgical implants or collapsed vertebrae at the level of the ROI, as these could influence the measurement. In a collapsed vertebra, the density might be increased due to the collapse, and not necessarily due to the RT, so the measurement of BMD could be influenced false-positively. Patients' medical records were used to collect patient baseline and treatment characteristics. These data included primary tumor, location of metastases, radiotherapy fractionation scheme, and the use of bisphosphonates.

Measurements

BMD was measured using a circular ROI in the axial plane of the CT images with an approximate diameter of 5 mm, dependent on CT voxel size. The center point of the ROI was set manually on the estimated 3D-centroid of the osteolytic lesion (Fig. 1). The ROI, as established in the first examination, was also used for the follow-up examination. Thus, the placement of the ROI on follow-up was identical to the location of the ROI on baseline. Due to the expected change in size and border of

the metastasis, a single ROI was considered more reliable than the delineation of the whole metastasis. Independent of tumor size and vertebral characteristics, one ROI was set per vertebra. If a patient had multiple affected vertebra treated with RT, a ROI was set for each vertebra. These measurements were executed the same way for all patients, assuring paired measurements of the metastatic lesions.

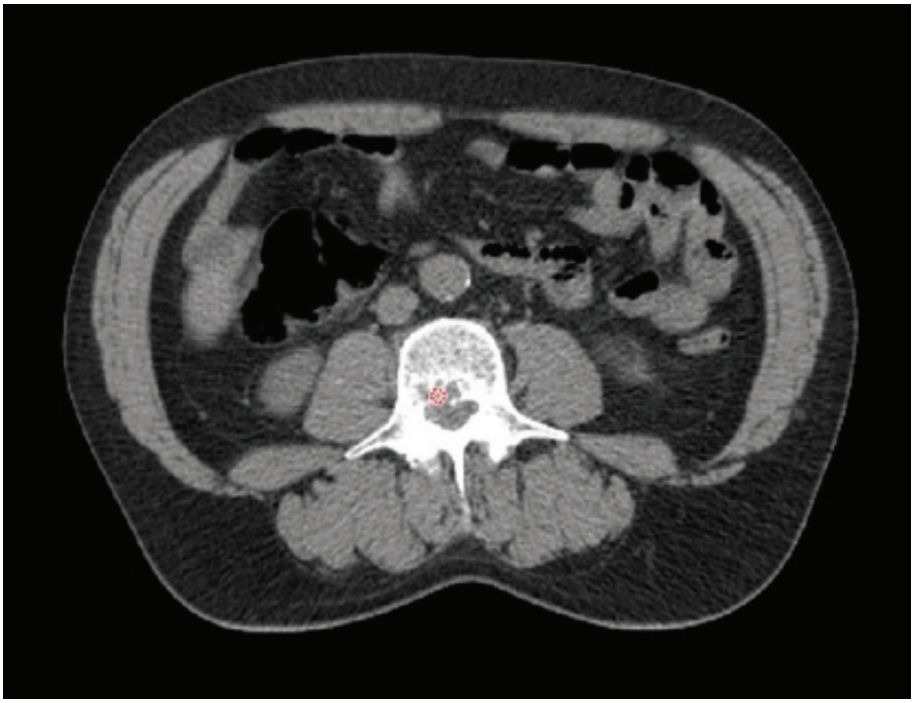

Figure 1. Example of placement of the region of interest (ROI) to measure bone mineral density

A reference measurement was performed in each patient if present on the CT images. For this measurement, a vertebra without any metastases two levels cranial to the lesion, and outside the irradiated area, was chosen. The placement of the ROI for the reference measurement was placed on an anatomically similar location in the vertebra as the ROI in the metastasis. In the case of a fracture, the presence of osteosynthesis material, or other anomalies, the adjacent cranial vertebra was selected. The reference measurement was used to estimate the effect of e.g. (disuse) osteoporosis, use of bisphosphonates, or effects of any systemic therapy on BMD.

All measurements were performed by the same observer (TV) who was not blinded for patient characteristics and outcome during assessment of scans. A random sample of ROI placement in 15 patients was assessed again by four observers to

check for accuracy of the observer's measurements: an orthopedic surgeon (JJV), a radiation oncologist (WSCE), a PhD-candidate of the department of radiation oncology (BJP) and a radiologist in training (WF).

Outcome

The primary outcome of this study was the change in mean HU in the ROI, compared between baseline scan before RT and the follow-up scan(s) in the three months following radiotherapy, and compared with the reference ROI. Secondary outcome was the change in HU in the ROI at any point in time during follow-up. In addition, clinical factors such as primary tumor and the use of bisphosphonates associated with change in HU, were evaluated.

Statistical analysis

The difference in mean HU between two separate points in time was analyzed with a paired T-test. The difference in mean HU between metastatic lesions and reference vertebrae was analyzed with a Welch T-test. A T-test was performed to analyze the association between the use of bisphosphonates and receiving five fractions and less, or more than five fractions. In addition, a Kruskall-Wallis test was performed to analyze the change in BMD and the differences between primary tumor histology. Data were analyzed using SPSS, IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp (22).

Results

Demographic data

Out of the 1025 patients available in the PRESENT database, 215 patients (21%) had spinal metastases and the baseline and follow-up CT scans available within our institution. Of these patients, 195 (91%) received RT, and 119 (55%) had at least one osteolytic spinal lesion. Of these 119 patients, 70 patients were excluded because of unsuitable baseline or follow-up scans in which the ROI was not completely visible, 12 because of osteosynthesis material at the ROI, and 4 because of a pathological fracture at the ROI. Two patients with multiple myeloma were excluded due to the date of first follow-up being more than 36 months after RT. There were no patients who had undergone reirradiation. This resulted in a study group of 31 patients, with 49 osteolytic metastases eligible for analysis (Table 1).

Table 1. Baseline characteristics

Age at baseline, median (IQR*)	**58 (53-63)**
Sex, n (%)	
Male	17 (55)
Number of bone metastases, n (%)	
1	12 (39)
2	13 (42)
3	4 (13)
4	1 (3)
5	1 (3)
Primary tumor, n (%)	
Breast	8 (26)
Kidney	5 (16)
Lung	4 (13)
Prostate	4 (13)
Esophagus	3 (10)
Other	7 (23)
Location of metastases in the spine**	
Cervical	3 (16)
Thoracic	26 (53)
Lumbar	16 (33)
Sacrum	4 (8)
Radiotherapy scheme***, n (%)	
1x 8Gy	24 (47)
10x 3Gy	13 (27)
1x 18Gy	3 (6)
5x 4Gy	6 (12)
Other	3 (6)
Bisphosphonates during RT*, n (%)	13 (42)
Chemotherapy during RT*, n (%)	13 (42)
Corticosteroids during RT*, n (%)	24 (77)

Percentages may not add up to 100% due to rounding
* IQR: Inter quartile Range, RT: radiotherapy
**Some patients had metastases on multiple sites
*** Some patients received multiple RT schemes

Remineralization

Mean density of all osteolytic lesions at baseline was 71.4 HU (95% CI 61.1–81.7). A total of 13 patients (42%) had a follow-up CT scan within three months after RT, in 8 patients a reference vertebra was available for measurements. The median interval between pre-RT and follow-up CT scans within this group was 1.9 months (interquartile range (IQR) = 1.5–2.7) In affected vertebrae, the bone density increased with 64.2 HU (95% CI 9.3–73.6; p= .04; Table 2) compared with a non-significant decrease in the reference vertebrae of -3.2 HU (95% CI -33.9–27.4; p= .84; Table 2). The difference at baseline between metastatic lesions and reference vertebrae was -165.8 HU (95% CI -348–16.5; p=.07; Table 2), and -92 HU after RT (95% CI -192.7–8.5; p=.07; Table 2).

Table 2. Change in BMD at follow-up, three months after radiotherapy

	N	Mean difference in HU (95% CI)	Change (in %)	P-value
Change in BMD* after RT* in:				
Metastatic lesions	13	64.2 (9.3–73.6)	203	0.04
Reference vertebrae	8	-3.2 (-33.9–27.4)	99	0.84
Difference between reference vertebrae and metastatic lesions:				
Before RT*		-165.8 (-348.0–16.5)		0.07
After RT*		-92.0 (-192.7–8.5)		0.07

p-value is based on a Welch t-test. A p-value <0.05 was considered statistically significant
* BMD: Bone Mineral Density, RT: Radiotherapy, HU: Hounsfield Units

Of all available scans and patients up to two years after radiotherapy, the median time between RT and follow-up imaging was 7 months (IQR 3–17) for metastatic lesions and 7 months (IQR = 3–18) for reference vertebrae as the reference vertebra was not available for ROI placement on all follow-up scans. The difference between baseline and follow-up BMD for metastatic lesions was 146.9 HU (95% CI 68.4–225.4; p<.01; Table 3) and 19.1 HU for the reference vertebrae (95% CI -47.9–86.0; p=.58; Table 3). At baseline, the difference between reference vertebrae and metastatic lesions was -194.1 HU (95% CI -276.2– -112.0; p<.01; Table 3) and after RT the difference was -50.3 HU (95% CI -119.6–990; p=.52; Table 3, Fig. 2). During the quality check by four raters of the random sample of measurements in 15 patients, there was complete agreement on the placement of the ROIs.

Table 3. Change in mean BMD in all available follow-up scans.

	N	Mean difference in HU (95% CI)	Change (in %)	P-value
Change in BMD* after RT* in:				
Metastatic lesions	49	146.9 (68.4–225.4)	306	<0.01
Reference vertebrae	31	19.1 (-47.9–86.0)	107	0.58
Difference between reference vertebrae and metastatic lesions:				
Before RT*		-194.1 (-276.2– -112.0)		<0.01
After RT*		-50.3 (-199.6–99.0)		0.52

p-value is based on a Welch t-test. A p-value <0.05 was considered statistically significant.
* BMD: Bone Mineral Density, RT: Radiotherapy, HU: Hounsfield Units

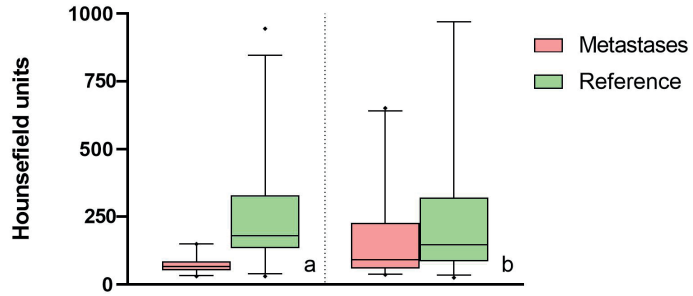

Figure 2. Comparison of mean HU between the metastases and reference vertebra before RT (a) and after RT (b).

Factors associated with remineralization

In the T-test analysis, lesions in patients using bisphosphonates showed a mean 133.5 HU larger increase in bone density compared with lesions in patients who did not (194.1 HU versus 60.6 HU; p< .01; Table 4). The proportion of patients using bisphosphonates did not differ between primary tumor types (Supplementary Table 1). Lesions in patients treated with more than five fractions showed a greater, but non-significant, change in HU compared to lesions treated with less than five fractions (145.8 versus 100.5; p= .12; Table 4). Metastases from primary tumors located in the breast, lung and kidney showed the largest increase of BMD (p=0.05).

Table 4. Factors associated with change in BMD after radiotherapy.

			Change in mean BMD*	
		N		p-value
	Bisphosphonates use			
Metastatic lesion	Yes	26	194.1	
	No	23	60.6	0.01*
Reference vertebra	Yes	23	34.7	
	No	12	7.2	0.15
			Lesion	
Number of fractions	1 to 5	35	100.5	
	More than 5	14	145.8	0.12
Primary tumor	Breast	13	181.4	0.05*
	Kidney	9	132.2	
	Prostate	6	26.9	
	Lung	4	148.1	
	Other	17	23.5	

p-value based on a univariable t-test for the change of BMD after use of the bisphosphonate during RT or in the reference group, number of fractions, and on a Kruskal-Walis test for the primary tumor comparison. *A p-value <0.05 was considered statistically significant.

Discussion

In the present study, we found that bone mineral density (BMD) increased significantly in osteolytic lesions after radiotherapy, while this did not occur in the unaffected, non-irradiated adjacent reference sites. The use of bisphosphonates was associated with a further increase in remineralization. In addition, the primary tumor was of influence on the degree of remineralization. Remineralization did not differ among patients receiving five or more fractions compared with treatment with less than five fractions.

This is one of the first studies comparing changes in BMD between irradiated vertebrae and reference vertebrae outside the radiation field. Our finding of the positive effect of RT on BMD is in line with previous studies. In a recent study, Jensen *et al.* analyzed the change of BMD, based on a change in HU, in patients with spinal metastases. In their study, 117 vertebrae were analyzed, including a control vertebra that was outside the 50% isodose, to adjust the BMD measurement of the lesion.(23) In the study by Jensen *et al.* the (lack of) change in BMD in the reference vertebra was used for the adjusted density change, but was not reported separately. Metastases came from various primary tumors, and received various dose and fractionation schedules. Jensen and coauthors found a density change of 104% ($p<.0001$) in the

unadjusted and 102% in the measurement adjusted for the control measurement within a median follow-up of 14 months. In contrast to our study, Jensen e*t al.* only included patients with a follow-up of >9 months. In addition, our study also shows an early effect on BMD as we saw remineralization within three months. *Foerster et al.* assessed the change in BMD after RT in 135 spinal metastases in 115 patients with breast cancer. Patients received 30 Gy in 10 fractions, 35 Gy in 14 fractions or 20 Gy in 2 fractions. Mean BMD was 194.8 HU (SD 123.0) at baseline. Mean BMD increased by 146 HU after 3 months (p.0001) and 250 HU after 6 months (p<.0001). They also confirmed that BMD did not change significantly in a neighboring unaffected vertebra receiving radiotherapy (24). Wachenfeld *et al.* examined remineralization on CT in 14 patients with vertebral metastases from lung cancer, treated with a total dose of 30 Gy to 36 Gy in 2 fractions. In the published abstract, Wachenfeld and coauthors found a significant increase in BMD in lytic lesions six weeks after RT, increasing further to 150% at three months (25). McDonald *et al.* analyzed the effect of stereotactic body radiation therapy (SBRT) on lytic non-spine bone metastases (12). The BMD was assessed in 22 cases, with a median follow-up of 7 months after RT. The change relative to baseline in median BMD for all lytic lesions was 104%, 139%, 188% and 186% after respectively 3, 6 and 9 and 12 months. At 1 year after RT, there was a decrease in BMD in only 3 out of 22 lesions. *Sprave et al.* performed a secondary analysis on the data from their trial, comparing pain response after conventional RT vs SBRT for painful bone metastases. In this secondary analysis, 46 patients were available for evaluation at three months, and 39 at six months (26). They found a significant increase after three and six months, an increase of 33.8 HU and 72.1 HU respectively in the conventional RT arm and an increase of 64.0 HU and 97.5 HU respectively in the SBRT arm (p=.01 for all within group changes). Moreover, no between-group difference was observed at three or six months, p=.63 and p=.33 respectively). Furthermore, they found a higher number of vertebral fractures six months after SBRT compared to conventional RT, 28% vs 5% respectively, p=.054 (27). Our study confirmed the occurrence of remineralization after RT, relative to a non-irradiated reference. The latter is important to correct for the major effect that systemic therapies and/or increased physical activity following effective palliation can have on the BMD of (non-)irradiated vertebrae during follow-up. As the BMD in unaffected, non-irradiated adjacent reference sites did not significantly increase while the BMD did increase in irradiated affected lesions, this effect is suggested to be attributable to radiotherapy.

Remarkably, despite previous studies finding an increase in BMD after radiotherapy for lytic spinal metastases, the baseline mean HU for the lesion was different in all these studies. In this study, we found a mean BMD of 71.4 HU (95% CI 61.1–81.7). In the study by Sprave et al. this was 178.5 (SD 74.4) and in the study by Mcdonald et al. the baseline mean HU was 92.5 (95% CI: 54.7 to 130). While data are limited, it may be concluded that remineralization occurs even with higher baseline BMDs

(12,26). The difference in baseline mean HU could be due to the difference of ROI placement. In the study by Sprave et al., a ROI was placed in the tumor while in the study by Mcdonald et al., the whole lesion was contoured.

Results of studies on the effects of RT on bone formation by osteoblasts and bone resorption by osteoclasts are conflicting, and the cellular mechanism of remineralization is not well known (15). Studies found the osteoblast activity to deteriorate after RT, while others found osteoblasts to be resistant to RT, with low dose RT even promoting proliferation of osteoblasts. In addition, the effects of RT on osteoclasts are ambiguous too. While RT could decrease osteoclasts activity, and therefore decrease bone resorption, RT could also increase osteoclast activity (15). In the healthy physiological state, the interaction between osteoblasts and osteoclasts is finely balanced and increased osteoclast activity induces increased osteoblast activity (28). It could therefore be hypothesized that after RT-induced destruction of tumor cells, the disturbed bone turnover – under the influence of tumor secreted cytokines in the micro-environment – may return to normal, with osteoclasts actively resorbing damaged bone and osteoblasts responding accordingly with increased activity to form bone locally (29). In the systematic review by Groenen et al., it was shown that there was an increase in BMD and trabecular bone in animal studies (30).

In agreement with the current study, Foerster *et al.* reported an increased remineralization after RT in patients using bisphosphonates (24). At 3 months after RT an improvement of 157.5 HU was observed in the bisphosphonate group, versus an increase of 52.2 HU in the non-bisphosphonate group (p=.01). In an animal model with osteolytic metastases, Krempien *et al.* observed an increase in BMD at 42 days after RT (p=.001), but only in the animals receiving bisphosphonates (3). Krempien *et al.* showed a significantly better-preserved bone microstructure in the pre-RT bisphosphonate group compared with the other two groups (p<.001). They hypothesized that an increased or preserved bone microstructure leads to an increased weight bearing capacity. A loss of the microstructure leads to increased formation of fibrous scar tissue (3). The use of bisphosphonates can preserve the structural integrity by the inhibition of bone resorption, and accordingly improve the ability of osteolytic lesions to remineralize after RT. Our study found a strong positive association between the use of bisphosphonates and remineralization. After RT, the lesions in patients receiving bisphosphonates showed a greater increase in BMD compared with the patients not receiving bisphosphonates. For the reference vertebrae, this effect of bisphosphonates was not observed. This supports the hypothesis that bisphosphonates contribute to remineralization of lytic bone metastases especially when combined with RT (3). Due to the limited number of patients included in this study, the independent effect of RT and use of bisphosphonates could not be assessed in multivariate analysis, and remains to be evaluated in future research.

We found a non-significant higher degree of remineralization in patients who underwent a radiation schedule with more than five fractions. The total RT dose in RT schedules below five fractions was under 20 Gy, compared with over 20 Gy in RT schedules with five fractions or more. A prospective study by Koswig *et al.* compared patients with fractionated (10x 3Gy) and single dose (1x 8Gy) (31). After 6 months, a significant difference in BMD was observed between patients in the fractionated group of 173% compared with a BMD increase of 120% in the single dose group. Nonetheless, this increase was only observed in patients with breast cancer (19,31). In a multivariable analysis, Stölting *et al.* found a trend towards increased remineralization for RT administered five times a week compared with 1–4 times a week (OR 8.4; p=.054), a total RT dose was not specified in this analysis (16). In addition, in the same analysis they found a total dose of 50 Gy or more, compared with 30 Gy or less, to be associated with increased remineralization (17). In the same way, Sprave et al. found a significant difference between short course (≤10 fractions) and long course (>10 fractions) in the proportion of patients who went from an unstable vertebra at baseline to a stable vertebra three months after RT. Six months after RT, however, this difference was not found (32). It is therefore not clear whether the increased remineralization can be contributed to a more fractionated scheme or a higher total dose.

The primary tumor origins may have substantial influence on the potential for remineralization after RT. Koswig *et al.* assessed the association between primary tumor and the magnitude of remineralization. In a patient group receiving a fractionated scheme of 10× 3Gy for (spinal) bone metastases originating from various primary tumors, lesions showed increases in BMD of 184% for breast cancer, 174% for prostate cancer, 147% for kidney cancer and 138% for lung cancer respectively, although these differences were not statistically significant. Only when multiple primary tumors were put together, a significant difference was found for the combined groups breast/prostate, and lung/kidney (p=.02). This could be due to a lack of power with their number of patients (21). Another study by Macdonald *et al.* distinguished between renal cell carcinoma (RCC) and 'other' primary tumors. Lesions from RCC showed an ongoing decrease in BMD during initial follow-up and this decrease stopped at approximately 12 months after RT (18). In contrast to the study by Macdonald *et al.*, in the present study metastases originating from the kidney also showed remineralization after RT.

The main limitation of this study is the limited sample size, with 31 patients with 49 lytic spinal metastases and follow-up scans available. Furthermore, the retrospective design of this study hindered follow-up as we were dependent on follow-up scans obtained during daily clinical practice. To obtain more robust data, follow-up CT scans at predetermined time intervals would be highly useful. Furthermore, it is still unknown whether remineralization of bone actually

improves bone strength and, ultimately, spinal stability, and could become a viable alternative to surgery in a selected group of patients with potential instability (SINS score 7-12).(10) Future research should be focused on the restoration of mechanical integrity after radiotherapy.

Conclusion

Radiotherapy of lytic spinal metastases is positively associated with increased bone mineral density at a median follow-up of seven months. Bisphosphonates is associated with increased remineralization in lytic spinal metastases after RT. Improvements in mechanical integrity and a possible reduction in surgical interventions for metastatic spinal disease may be achieved after remineralization and are the topic of further study.

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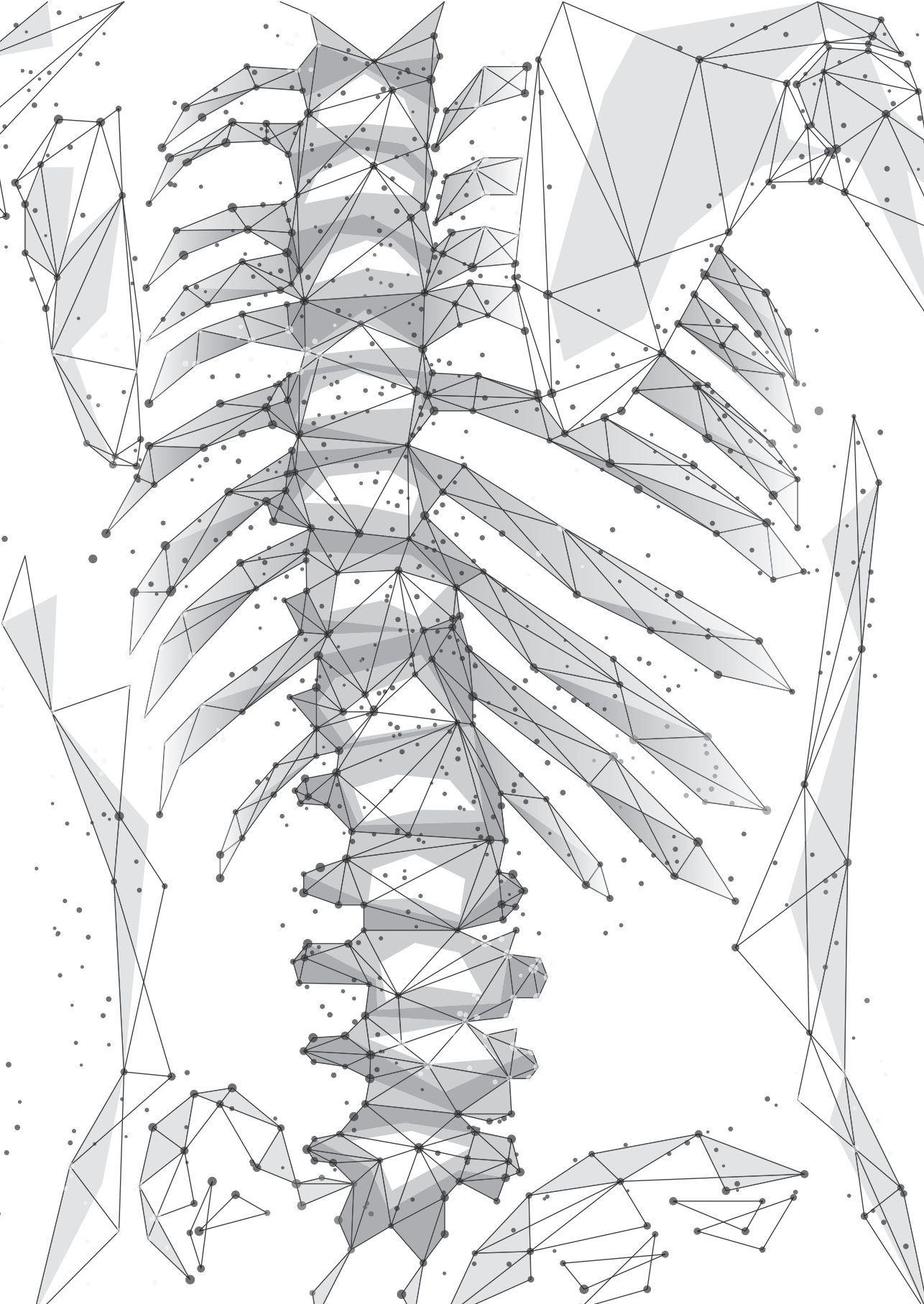
Supplementary material

Supplementary table 1. Use of bisphosphonates between primary tumors, shown as number of bone metastases per group.

	Bisphosphonate use n(%)	
Primary tumor	no	yes
Breast	3 (23)	10 (77)
Prostate	6 (100)	0 (0)
Kidney	3 (33)	6 (67)
Lung	4 (100)	0 (0)
Other	7 (41)	10 (59)



CHAPTER 7

Summarizing discussion

Due to earlier detection and improved treatment, cancer patients' life expectancy has improved substantially over the past decades.(1) Patients with cancer are living longer, which means they are longer at risk of developing bone metastases. Up to 70% of the patients dying of cancer have developed bone metastases.(2–4) Bone metastases have a high impact on the patient's life as they often cause pain, reduced mobility due to pathological fractures and/or hypercalcemia which can cause (among others) cardiac arrythmias, renal failure and pancreatitis. If bone metastases are present in the spine, they can cause spinal instability, compression of the spinal cord or cauda equina.(5) The life expectancy of patients with bone metastases is generally limited. Over 80% of patients dies within two years, with a median survival of just under eight months. However, a small, but growing number of patients experience a longer survival, and may be alive ten years after the diagnosis.(6,7)

This thesis has addressed the selection for, and effects of, innovative approaches of radiation treatment for patients with symptomatic bone metastases. New treatment options require evaluation of the effects of the treatment as well as optimal patient selection for these treatments. Treatment goals differ across patients. In patients with a limited life expectancy, improving or preserving quality of life is the main focus, aiming at pain reduction and regaining function and mobility. But in patients with longer life expectancy, obtaining local tumor control may be equally or even more important. In addition, not all patients are fit enough to undergo extensive treatment such as surgery. It is therefore necessary to select the optimal treatment, based on a patient's preferences, performance status, and life expectancy. The main focus of this thesis is to provide insights into optimal treatment of symptomatic bone metastases in the secondary and tertiary care. In this section, the main findings of this thesis will be addressed and some of the remaining challenges and perspectives on the treatment of patients with bone metastases will be discussed.

Key findings

In this thesis effectiveness of stereotactic body radiation therapy (SBRT) and conventional radiotherapy (cRT) were compared in patients with painful bone metastases. After treatment with SBRT or cRT, a comparable pain response (*Chapter 4)* and comparable improvement of quality-of-life(QoL) scores *(Chapter 5)* was observed. Furthermore, we found that the TwiCs design was a feasible design to include patients in the palliative setting and gave an insight in patients' acceptability of an innovative intervention (*Chapter 4*). In *chapter 6, w*e found that bone mineral density of the vertebra increased after radiotherapy for spinal. Finally, we demonstrated that body morphology could be used to improve the estimation of life expectancy in the patients treated with radiotherapy for spinal

metastases (*Chapter 2)* and patients who underwent surgery for the spinal metastases *(Chapter 3).*

The use of body morphology for patient selection and treatment strategy

Generally, patients with bone metastases are treated in a palliative setting, with focus on maintaining and/or improving the quality of the patient's remaining life. When a patient's life expectancy is less than three months, surgical treatment is not an option as the patient's quality of life (QoL) is hampered too much by the impact of surgery, recovery and revalidation to justify the treatment.(8) In the same way, different radiotherapy modalities and schemes, conventional of stereotactic, short or long-course, have different levels of burden. The estimation of the life expectancy, however, is full of challenges as multiple factors influence the life expectancy. Currently, to predict survival of patients with spinal metastases, models often include the primary tumor, performance score and the presence of visceral and/or brain metastases.(9–11) The prognostic value of these models is limited however.(11) We sought to improve the estimation of a patient's prognosis by using body morphologic factors. In advanced cancer patients, a loss of fatty and muscle tissue is seen, summarized as cachexia.(12,13) Cancer cachexia, a complex and multifactorial wasting syndrome, is associated with decreased physical functioning and overall survival.(12,13)

In *chapter 2*, studying body morphology in patients undergoing radiotherapy for bone metastases, we found that muscle density has an added prognostic value whereas the volumes of subcutaneous or visceral fat did not. In contrast, in patients undergoing spinal surgery, an increased volume of visceral fat was associated with an increased chance of survival within three months after surgery *(chapter 3)*. This difference could be a result of patient selection. Presumably, the patients in the surgery group had been in a better general condition and body morphology changes as the disease progresses and the patients general changes condition. This difference does show the need for further, prospective, research in multiple departments and centers.

Bollen et al. tested the predictive value of the six most often used models and showed that the C-statistic ranged from 0.44-0.70, meaning the model can make a correct distinction between patients 44-70% of the cases, based on the variables in the model. (10,11,14–17) This predictive value is considered to be moderate up to 0.7. *Chapters 2* and *3* might improve the estimation of a patient's prognosis combined with existing prognostic models.

Machine learning was used to develop a prognostic model for survival of patients undergoing surgery for spinal metastases.(10) A stochastic gradient boosting model was developed were multiple decision trees (weak learners) were combined sequentially, where every weak learner improves the previous weak learner. For the development of this model, 732 patients from a retrospective dataset were included. Clinical factors such as sex, body mass index, Charlson Comorbidity Index and primary tumor were taken into account. Alongside these variables, this model included hematologic factors such as blood cell counts, albumin and creatinine. The model was internally validated and a c-statistic of 0.88 was found for predicting 90-day survival and 0.89 for one year survival. Of note, this model has not (yet) been validated externally.

Alcorn et al. developed a prediction model for survival of patients with symptomatic bone metastases undergoing radiotherapy (18), using the random forest machine learning method. A random forest consists of multiple decision trees, simple models using multiple successive questions to form a decision, e.g. a patient dies or not within three months. The outcome, however, is often inaccurate and prone to overfitting. In a random forest model, the outcomes of multiple random decision trees are merged into a single outcome to create a more reliable outcome. The study contained 397 patients and 27 variables were identified: clinical factors such as primary tumor, weight loss and performance score as well as blood cell count and (type of) systemic therapy. Internal validation was performed and c-statistics of 0.83 and 0.81 were found for the three-month and one-year survival respectively. In the external validation by Elledge et al., which was performed in the same center with data collected from three successive years, C-statistics were 0.86 and 0.78 for the three months and the one-year survival respectively.(19)

Unfortunately, prediction models, such as the Tokuhashi, Tomita and Bollen models, were based on retrospective data of patients who either underwent surgery or radiotherapy for symptomatic metastases.(15,16) The Tokuhashi and Tomita models are based on patients who underwent surgery, while in the Bollen model 95%, of the patients underwent radiotherapy only. This could have introduced selection bias as patients who underwent surgery were deemed fit enough for surgery. In contrast, patients who underwent radiotherapy may not have been fit enough for surgery. Therefore, as the models are based on a population of patients who underwent surgery or radiotherapy, the generalizability is limited.

Chapters 2 and 3 showed that body morphology has the potential to improve prognostic models. Future studies developing prognostic models could benefit from a more heterogeneous group of patients, where all patients with bone metastases are included prospectively and at multiple departments. As patients with spinal metastases undergo (multiple) CT scans preoperatively or before RT,

these data could be used for research purposes (ideally with informed consent of patients). Weston et al. and Kim et al. showed that the measurements of visceral and subcutaneous fat and muscle can be done (semi-) automatically.(20,21) Developing a model prospectively, could help both the patients and treating physicians in the treatment considerations. It should be taken into consideration, however, that a model should not be too complicated in order to be implemented in daily practice.

Evaluating innovative treatments

To compare the effect of cRT and SBRT on pain and QoL scores in patients with painful bone metastases, the VERTICAL trial (comparing conVEntional RadioTherapy with stereotactIC radiotherapy in patients with spinAL metastases) was executed. The VERTICAL trial was the first trial in the palliative setting following the Trials within Cohorts (TwiCs) design. Effectiveness of new treatments are often evaluated in classic RCTs, where patients are informed about the trial and asked informed consent to be randomized to either the standard of care or the new treatment. Only after consent and randomization, patients are informed which treatment they are going to receive. Patient accrual in classic RCTs is notoriously challenging.(22) For example, palliative patients could be hesitant to participate in a trial if they have a risk of being disappointed when randomized to the control arm.(22–24) Furthermore, participating in a trial comes with a cost in terms of both time and energy, which may be too much for patients with bone metastases.

With TwiCs, a two-stage informed consent procedure is used.(25) In the first stage, at cohort-entry, patients are asked for consent for the use of their data and filling out patient reported outcome measures. In addition, patients are asked for their consent for randomization into future RCTs executed within the cohort. When a patient is eligible and randomized to the control arm, they are not contacted. When a patient is randomized to intervention arm, they are asked for informed consent to undergo the intervention, i.e., second stage informed consent. This procedure is more patient centered because patients only receive information that is relevant and they don't receive information about treatments they cannot receive. In addition, the two-stage informed consent procedure aims to prevent disappointment bias. Disappointment bias could occur when a patient is informed about an experimental/innovative treatment, get hopes for an innovative treatment, and is then randomized to the control arm. Finally, the two-stage informed consent increases efficiency of accrual. With patients are already included in the PRESENT cohort, there is a 'patient pool' which provides patient information from which patients can selected for and be included in the trial. Furthermore, as patients in the control arm are not informed on the trail they will not drop-out due to refusal. These factors improve the efficiency of the accrual.

The VERTICAL trial illustrated several theoretical advantages of TwiCs. During the time of enrollment for VERTICAL, more than 900 patients were enrolled in the PRESENT cohort, 178 of whom were eligible for the VERTICAL trial. Of the eligible patients, 60% was included in the trial, - i.e. 110 patients were included in a single center in a timespan of four years *(Chapter 4).*(26) This is quite extraordinary, as from other comparable trials, we know that accrual is challenging in this vulnerable patient population. The RACOST trial, a Dutch multicenter trial aimed to include 386 patients with spinal metastases in five centers, was terminated early due to lack of accrual.(22) The RTOG 0631 trial was a large multicenter trial that took nine years to include 339 patients with spinal metastases in 38 study locations in three countries. (27) Lastly, Sahgal et al. included 229 patients in 18 study locations, which took over 3.5 years.(28) In the same way, the multicenter, three-armed DEXA-trial, evaluating the effect of dexamethasone during and after RT to prevent pain flares, aimed to included 411 patients within two years.(29) However, after almost four years the study was completed with an inclusion of 295 patients. (30)

One of the particularities of the TwiCs design is selective refusal in the intervention arm, which is not present in the control arm. In the VERTICAL trial, a selective refusal of 27% was noted in the intervention arm, the main reason for the refusal was the waiting time until treatment. In the control arm, this refusal is not seen, as they were not aware they are part of a trial. This refusal is a doubled-edged sword. On the one hand, it provides valuable information on patients' willingness to undergo an innovative treatment. On the other hand it makes the study underpowered to show the anticipated difference. As described by Reeves and et al., drop-out and refusal observed in TwiCs, should be taken into account in the power-calculation. (31) To improve the power-calculation, performing a pilot study is recommended to help estimate the drop-out or refusal.

A larger trial by Saghal et al. included a total of 229 patients, whereof 223 patients completed treatment, 113 in the cRT arm and 110 in the SBRT arm.(28) Patients in the cRT arm received 20 Gy in five fractions and patients in the SBRT arm received 24 Gy in two fractions. SBRT was shown to be superior at both three and six months after treatment. At three months, 35% of the patients in the SBRT group and 14% of the patients in the cRT arm had a complete pain response. After six months 32% in the SBRT arm and 16% of the patients in cRT arm had a complete response. This trial is the first large trial which showed that dose escalation, distributed in two fractions, could improve pain response. (32) In their trial, the proportion of patients in the cRT arm with a complete response after three months, 14%, is comparable to the 13% of patients with a complete response we found in the VERTICAL trial. In addition, the proportion of patients with a complete response three months after SBRT was higher compared to the VERTICAL trial, 35% vs 9%.

In addition to the advantages of innovative treatments, adverse events must be considered for the choice of treatment. In the VERTICAL trial, no grade ≥ 3 side effects were seen in either the cRT or SBRT arm. Nguyen et al. and Sprave et al. found no differences in the proportion of patients with grade 1 or 2 side-effects after treatment between the cRT arm and SBRT arm.(33,34) In the trial by Sahgal et al., the proportion of patients with a grade ≥ 3 complication was comparable between the two treatment arms.

SBRT for bone metastases may induce a longer lasting effect on the pain reduction compared to cRT.(35) The pain duration could be measured in weeks with reduced pain or as Net Pain Relief (NPR), defined as the proportion of remaining time alive with improved pain scores for patients in the palliative phase. Unfortunately, solid data are still limited due to the limited number of trials with extended follow-up in combination with the limited overall survival of patients with bone metastases. Van der Ven et al. performed a retrospective, non- randomized analysis of the duration of patients receiving either conventionally fractionated 3-dimensional radiation therapy (3DCRT) or SBRT. They found a comparable median duration of pain response between the two groups, 23 vs 24 weeks respectively).(36,37) Spencer et al. used data from the Dutch Bone Metastases Study to analyze NPR. In their study among 539 patients, NPR was 56.6, meaning the patients had improved pain scores for the majority of their remaining life.

Future trials evaluating pain response after cRT and SBRT should take a longer follow-up into account but also show the course of the pain scores over time and include the NPR. This NPR could be taken into account in the treatment selection for patients with a generally good prognosis, as they could benefit more from a longer lasting effect.

Radiotherapy to prevent or substitute surgery for spinal metastases

Bone metastases cause a disbalance in the activity of the osteoclasts and osteoblasts, the bone resorbing cells and bone forming cells respectively.(38) In lytic spinal metastases, there is a net increased osteoclast activity.(39) This increased bone resorption may decrease the load bearing capacity of the bone and therefore can lead to pathological fractures and affect spinal stability.(40) When spinal instability is extensive, surgery may be necessary to stabilize the spinal column and prevent or improve neurological deficits. However, when there is limited mechanical instability or no neurological impairment, radiotherapy with or without systemic therapy might suffice for the treatment of symptomatic spinal metastases. (41–44). Radiotherapy could result in a renewed balance between osteoclastic and osteoblastic activity, and therefore the promotion of bone growth and restoration of bony architecture. The exact pathophysiological mechanisms behind this phenomenon, however, are unclear.(45,46)

Bone growth, and subsequent increased bone density, can be measured in Hounsfield Units (HU) on CT scans. HU is a linear coefficient measurement depicting density measured on x-ray. Bone HU values range from –300 to 2000, Patel et al. found a mean HU of non-osteoporotic vertebrae to be 195.7 (95% CI 171.1-220.0).(47,48)

In *chapter 6,* we found that after cRT for bone metastases, bone density increased significantly compared to baseline. An increased bone density was observed both within three months and at complete follow-up (median follow-up of seven months). Bisphosphonates contributed to this remineralization. We measured the change in bone density in a reference vertebra, a vertebra without metastasis and outside of the irradiated field, and found no significant change in bone density, even in patients who used bisphosphonates. Comparable results were seen in previous studies.(44,49,50). In the reference vertebra, no change in bone density was observed, which could mean that a healthy osteoclast-osteoblast balance remains intact after cRT. Mcdonals et al. found an increase of 138% three months and 186% twelve months after SBRT for lytic non-spine metastases mainly from renal cell carcinoma.(44)

In addition to these studies on BMD, Dimar et al., evaluated the load-bearing capacity of vertebrae and studied whether the size of a defect, such as a tumor, has an influence on this load bearing capacity.(51) In their study, cadaveric vertebrae were scanned to measure the bone mineral density and the cross-sectional area of the vertebrae. Pressure was applied to reference vertebrae and a vertebra in which a hole was drilled to mimic a metastasis. They found that the size of the defect did not influence the load bearing capacity. A decreased BMD and a smaller cross-sectional area were associated with a decreased load-bearing capacity.

Eggermont et al. prospectively evaluated the load-bearing capacity of the femur with femoral bone metastases.(52) In a patient specific finite element model, the load bearing capacity of the femur was simulated and the model was used to test at what load the femur would fracture. Next, prediction of the model, whether the femur of a patient would fracture or not, was compared to the clinical results. A total of 45 patients were included with 50 femoral metastases. Patients were included if they had a metastasis with a cortical involvement of ≤30mm and received 8Gy in a single fraction. Patients with cortical involvement of >30mm were referred for surgery. If a patient had cortical involvement of >30mm but a general condition too poor for surgery they received multifraction RT. Seven femoral fractures occurred, and the model had a sensitivity of 100% and specificity of 74%. The median time to fracture was 8 weeks (range 1-18).

Previous studies like the ones by Eggermont et al. and Dimar et al. showed the influence of a metastasis or defect on the load-bearing capacity of the femur or spine. It is unclear, however, whether an increased bone mineral density after radiotherapy also increases the load bearing capacity of the femur or vertebra. Hence, future studies could focus on the load bearing capacities of irradiated bone.

While multiple studies found an increase in the bone mineral density after RT, all were retrospective with varying follow-up times. To objectify the bone mineral density after RT, a prospective trial with a diverse population should be set up, with patients receiving follow-up CT scans to track changes over time. This could include a randomized study to compare the use of bisphosphonates or SBRT vs cRT and its impact on the remineralization. In a heterogeneous population, contributing variables to increased bone mineral density, such as primary tumor, can be assessed better compared to a retrospective study. It is possible to perform these follow-up scans at predetermined intervals. However, the time period during which the majority of the increase in bone mineral density occurred may be overlooked. It could thus be considered to perform these follow-up scans at more random time points in order to more easily detect when the majority of remineralization has occurred. If there is limited spinal instability, it is critical to determine how long it will take to achieve sufficient remineralization and increased spinal stability, as well as which patients will achieve this. The estimation of the time to attain sufficient remineralization should be taken into account in further trials. If the time to sufficient remineralization can be estimated, the expected remineralization can be taken into consideration in patient selection for a treatment. If it is expected beforehand that a patient will have sufficient remineralization after RT and therefore sufficient load bearing capacity, surgery might not be necessary and RT would suffice.

Bone metastases in primary care

Over the past decades, possibilities and responsibilities of care provided by the general practitioner (GP) have increased. For palliative care, the GP has become a pivot between the patient and secondary or tertiary care physicians.(53) A GP can oversee a patient's physical condition and complaints, and his or her QoL more easily than the radiation or medical oncologist because of the short lines of communication. While the choice of treatment is often not within the scope of the GP, consultation on the treatment of painful bone metastases with the radiation or medical oncologist or orthopedic surgeon is an important option for the GP.

One of the most common complaints in the GP practice is (lower) back pain. Only 1% of patients presenting with lower back pain in the GP setting have spinal metastases.(54–56) Therefore, it is challenging for GPs to distinguish between

benign lower back pain and pain caused by bone metastases. Also, information on bone metastases in the GP guidelines by The Dutch College of General Practitioners (Nederlands Huisarts Genootschap, NHG) is limited.

Nonetheless, early detection of bone metastases is crucial.(57) In the early stages of metastatic disease, patients can be treated with less invasive treatments such as systemic therapies or radiotherapy. When metastases become larger and induce spinal instability or neurological symptoms, surgical stabilization and/or decompression may be required.(57) In cases where surgery is indicated, patient's time in the hospital is shorter when a metastasis is detected early.(58) In addition to the benefit to the patients, timely treatment of spinal metastases is more cost-effective.(58)

One of the tools used for the recognition of bone metastases is the so called 'Red Flag' symptoms. In 2015, Van Der Linden et al. wrote a clinical lesson in *Nederlands Tijdschrift voor Geneeskunde* on diagnosing bone metastases and referral of patients in primary care. In their clinical lesson, they focused on the use of Red Flags for spinal metastases to improve the detection of bone metastases. These red flags include increasing and continuing pain as well as pain during the night.(59) Despite their effort, research by Van Tol et al. showed there still was a considerable delay in diagnosis and referral of patients with painful bone metastases.(60) This delay occurred on the side of specialists as well as the GP and the appropriate use of Red Flags was (very) limited.(60) The mean time from first consultation to referral was 40 days, with a median of 18 days. In patients with a known pre-existing malignancy physicians should be on the alert for complications of advanced malignancies. However, there was no difference in diagnosis or referral delay between patients with or without a known pre-existing malignancy. Another remarkable finding was the use of- and false reassurance by conventional radiographs, the latter finding presumably because the sensitivity of this imaging modality is low.(61,62)

The Cochrane Review by Henschke et al. showed that the diagnostic value of Red Flags is limited when a single Red Flag is used to raise the suspicion of a metastasis.(63) In an earlier systematic review by Henschke et al., a previous history of malignancy was the most informative factor with a pooled positive likelihood ratio of 23.7, which means that patients with back pain and a history of malignancy were 23 times more likely to have a spinal metastasis than patients without a known malignancy.(54) Currently, literature on the diagnostic value of Red Flags for spinal metastases is heterogeneous and of limited quality.(54,63) In a position statement by Finucane et al., weight loss was considered to be an important symptom as well.(64) One of the main problems of the diagnostic studies was the low prevalence of bone metastases in patients with low back pain in primary care with a range of 0%-0.66%.(63)

While the diagnostic value of Red Flags is limited, it is the only tool currently available for the identification on spinal metastases. Updating the 'NHG-standaarden' might be a good means to increase the knowledge on (spinal) bone metastases, the use of Red Flags, clear guidelines on referral and knowledge of the treatment of these metastases. In a practice pointer, Downie and et al. sought to improve the diagnosis and referral of patients with bone metastases in primary care.(65) They state that a patient with severe low back pain and a history of cancer is considered to have a spinal metastasis until proven otherwise. Patients with severe pain and loss of function were considered high risk for bone metastases, as well as a rapid onset, acute deterioration and progression over weeks. Furthermore, pain on palpation, metastases affecting other organs and hypercalcemia were considered risk factor for the presence of bone metastases. Downie et al. suggested to perform blood test including full blood count, calcium alkaline phosphatase and albumin. The use of plain radiographs is still advised during an initial investigation.

As the number of patients with bone metastases is expected to be increasing further, and the role of the GP is growing, it is of great importance to provide an adequate tool to better recognize bone patients with metastases. Future – larger – studies in the primary care setting could focus on finding additional red flags, such as bone turnover markers in blood or urine and serum calcium levels, or increasing diagnostic value by combining red flags.(66–68) The knowledge of GPs on bone metastases should be increased further by expanding the information on bone metastases in the 'NHG-standaarden'. Furthermore, every region should have regional oncologic-palliative framework for consultation purposes as well as training.

Closing Remarks

Better treatment of the growing group of patients with bone metastases are still needed. Proper evaluation of new techniques is crucial to preserve high standards of care and further personalize treatment. In an era where treatment is increasingly focused on the improvement of the quality of life, selecting the right treatment for a patient with bone metastases never has been more important.

This thesis emphasizes the many challenges that remain before we can truly deliver personalized treatment for patients with bone metastases. Hopefully, the knowledge generated in this thesis will help physicians and patients to decide on optimal treatment, together.

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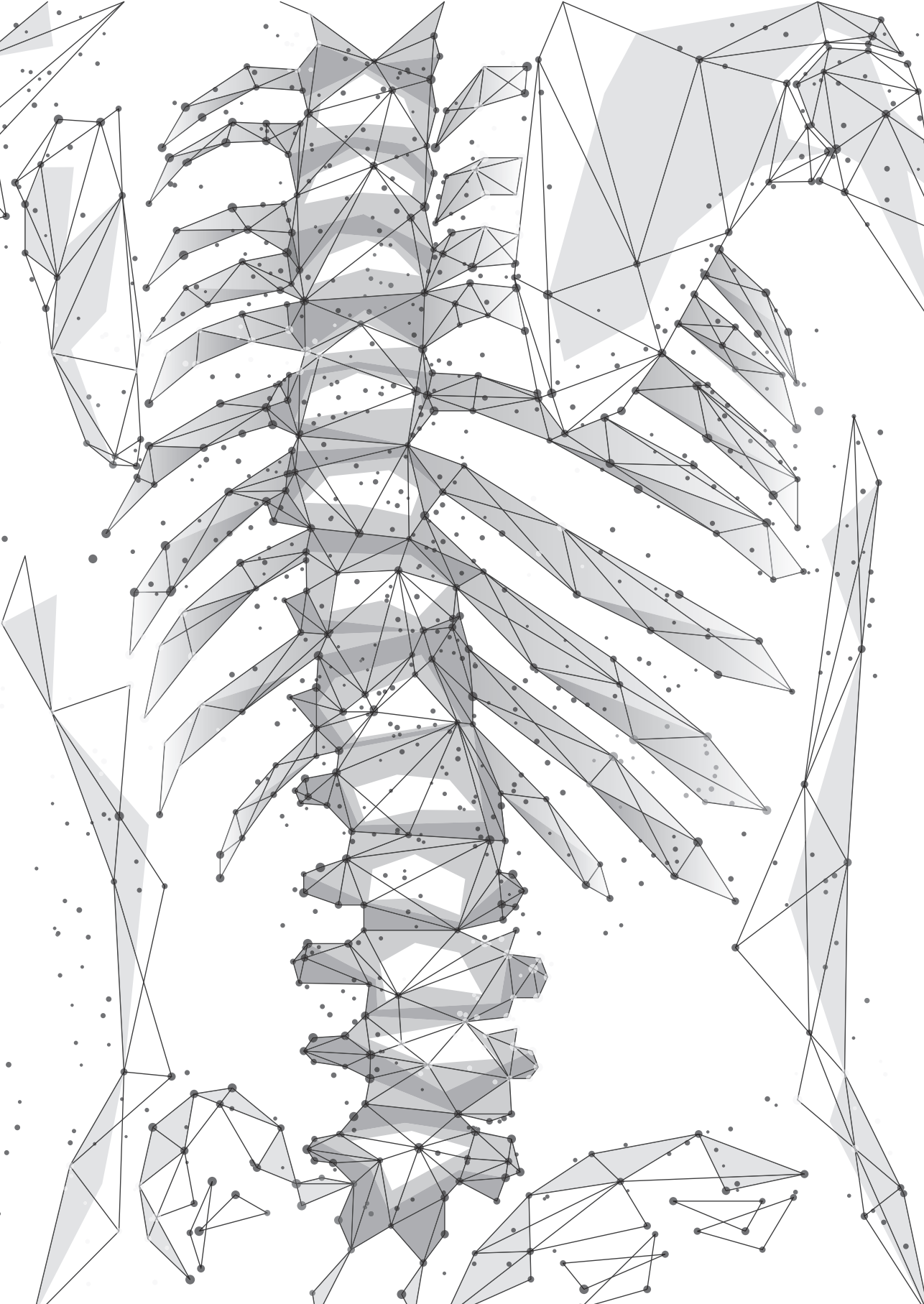

APPENDICES

Nederlandse Samenvatting

Inleiding

Het aantal patiënten met kankeruitzaaiingen naar de botten (botmetastasen) is de laatste decennia fors gestegen. Dit komt enerzijds door de toegenomen incidentie van kanker in het algemeen, maar ook door vroege opsporing en verbeterde behandelingen van kanker waardoor de levensverwachting is toegenomen. Als er sprake is van botmetastasen, wordt de ziekte als ongeneeslijk beschouwd. Botmetastasen hebben een grote impact op de kwaliteit van leven van de patiënt, voornamelijk doordat een botmetastase pijn veroorzaakt. Botmetastasen kunnen daarnaast ook de mechanische sterkte van het bot aantasten, waardoor er een vergrote kans op botbreuken ontstaat. Tevens, als een botmetastase in de wervel zit, kan deze druk geven op het ruggenmerg en hierdoor neurologische uitval veroorzaken.

De voornaamste focus van de behandeling voor patiënten met botmetastasen ligt momenteel op pijnbestrijding en (hiermee) verbetering of behoud van kwaliteit van leven. De standaardbehandeling is op dit moment conventionele radiotherapie. Hierbij zien we dat ongeveer 60% van de patiënten voldoende pijnverlichting ervaart. Als het bot te verzwakt is door een metastase, kan het nodig zijn om (eerst) te opereren.

Het voorspellen van de overleving

De behandeling van botmetastasen vereist een gepersonaliseerde aanpak. Voor elke patiënt en elke botmetastase moet een inschatting worden gemaakt welke behandeling het beste is. Dit is onder andere afhankelijk van de primaire tumor, locatie van de botmetastase, metastasen elders in het lichaam, de algehele conditie en verwachte overleving. Patiënten die nog enkele weken te leven hebben, hebben geen baat bij een intensieve of langdurige behandeling, zoals chirurgie en meerdere bestralingen. De tijdsduur totdat patiënten een vermindering van de pijnklachten ervaren of de bijkomende revalidatie is dan te lang voor de beperkte levensduur. De levensverwachting wordt geschat met behulp van predictiemodellen. Deze modellen gebruiken factoren zoals algehele conditie van de patiënt (samengevat in de Karnofsky Performance Score (KPS)), primaire kankersoort en eventuele uitzaaiingen naar andere organen en de ziektegeschiedenis van een patiënt. Echter is de nauwkeurigheid van de bestaande modellen beperkt. Maximaal 70% van de voorspellingen(c-statistic) of een patiënt nog leeft na enkele maanden tot maximaal twee jaar is correct.

In de afgelopen jaren is er onderzoek gedaan naar de rol van de lichaams-samenstelling in het voorspellen van de verwachte overleving. Deze lichaams-samenstelling, die ons

meer verteld over de algehele conditie van een patiënt, bestaat onder andere uit het meten van vet en spieren. Voor een vetmeting wordt op een CT-scan het vetoppervlak gemeten en onderscheid gemaakt tussen buikvet rondom de organen en het onderhuidse vet. Voor een spiermeting wordt op een CT-scan gekeken naar het totale spieroppervlak en de spierdichtheid. Bij elke patiënt met een wervelmetastase wordt een CT-scan gemaakt voor behandeling, deze CT-scan kan gebruikt voor de meting van de lichaamssamenstelling.

Het gebruik van de lichaamssamenstelling voor het voorspellen van de levensverwachting was nog niet onderzocht voor patiënten met botmetastasen. De toegevoegde waarde van de lichaamssamenstelling voor het voorspellen van de levensverwachting hebben we onderzocht in **hoofdstuk 2 en 3.** In **hoofdstuk 2** zijn 310 patiënten die deelnemen aan het PRESENT-cohort geselecteerd. Alle patiënten die in het UMC Utrecht worden verwezen voor bestraling van botmetastasen worden gevraagd voor deelname aan het PRESENT cohort, mits er een bewezen primaire kanker is, er sprake is van botmetastase(n) en bestraald wordt voor deze metastase(n). Binnen PRESENT wordt toestemming gevraagd voor het verzamelen van klinische informatie over de patiënt en voor het toesturen van kwaliteit-van-leven-vragenlijsten voorafgaand aan de bestraling en op vaste momenten na de bestraling. Bovendien kunnen patiënten toestemming geven om in de (nabije) toekomst eventueel geselecteerd te worden voor gerandomiseerde studies.

Voor de studie in hoofdstuk 2 zijn alle patiënten geïncludeerd waarvan een CT-scan beschikbaar was op het niveau van de buik. Op het niveau van de derde lendenwervel werd de lichaamssamenstelling gemeten want dit geeft de beste schatting van het totale lichaamsvet en spieroppervlak. In deze studie zagen we dat de algehele conditie van de patiënt (KPS), primaire tumor en spierdichtheid invloed hadden op de overleving binnen drie en twaalf maanden. In **hoofdstuk 3** is dezelfde analyse uitgevoerd in een groep van 75 patiënten die vanwege een botmetastase in de wervelkolom een chirurgische ingreep heeft ondergaan in het John Hopkins instituut (Baltimore, Verenigde Staten). Naast de lichaamssamenstelling, zijn in deze studie ook de Body Mass Inbex(BMI), motorisch functioneren en overige ziektegeschiedenis samengevat in de Charlson Comorbidity Index onderzocht. In deze studie zagen we dat een groter onderhuidse vetoppervlakte geassocieerd is met een betere overleving binnen drie maanden. Tevens was een hoger BMI geassocieerd met een betere overleving binnen twaalf maanden.

Hoofstukken 2 en 3 laten zien dat het meten van lichaamssamenstelling mogelijk gebruikt kan worden om de voorspelling van de levensverwachting te verbeteren. Het model in hoofdstuk 3, liet een c-statistic zien tot 84%. Toekomstige studies en modellen zouden de bestaande modellen, kunnen combineren met metingen van de lichaamssamenstelling.

Evaluatie van nieuwe behandeltechnieken

In de jaren negentig is het gebruik van stereotactische radiotherapie voor botmetastasen voor het eerst beschreven. Met stereotactische bestraling kan een metastase nauwkeurig en met een hoge dosis worden bestraald. In de afgelopen decennia is bewezen dat het een veilige en effectieve behandelingsmethode is voor de bestrijding van pijn bij botmetastase. Het is echter een kostbare en tijdrovende behandeling en het is niet zeker of stereotactische bestraling ook beter is dan conventionele bestraling, welke minder tijd kost en minder kostbaar is. Er waren nog geen gerandomiseerde studies verricht die conventionele radiotherapie met stereotactische radiotherapie vergelijken of het gebied van pijnvermindering en verbetering van kwaliteit van leven.

De VERTICAL-trial is uitgevoerd volgens het Trials within Cohorts (TwiCs) design en werd uitgevoerd binnen het prospectieve PRESENT cohort. Voor de VERTICAL-trial werden 110 patiënten geïdentificeerd die voldeden aan de vereisten om mee te kunnen doen aan de studie. Aan 55 willekeurig geselecteerde patiënten is de behandeling met stereotactische bestraling aangeboden (de interventie arm), waarna ze deze konden weigeren of accepteren. De andere 55 patiënten werden behandeld met de standaardbehandeling, conventionele radiotherapie (controle arm). Zij werden niet geïnformeerd dat ze onderdeel waren van de trial.

In **hoofdstuk 4** worden de resultaten van de VERTICAL-trial op het gebied van pijnbestrijding besproken. In dit hoofdstuk kijken we ook naar het gebruik van TwiCs-design. Van de 55 patiënten die voor stereotactische bestraling geselecteerd waren en dit aangeboden kregen, zijn 26 patiënten behandeld met stereotactische bestraling. Van de 55 patiënten in de controle arm zijn 45 patiënten behandeld met conventionele radiotherapie. In de interventie arm heeft 27% procent van de patiënten de stereotactische bestraling geweigerd, onder andere door de langere wachttijd vergeleken met conventionele radiotherapie. In beide studiearmen was de vermindering van pijn na de bestraling vergelijkbaar, er waren geen ernstige bijwerking in een van de groepen. Ondanks dat een aanzienlijk deel van de patiënten stereotactische bestraling weigerden, wat een negatieve invloed heeft op de bewijskracht, kunnen we voorzichtig stellen dat stereotactische radiotherapie niet beter is dan conventionele radiotherapie.

Behalve het effect op pijn na de bestraling met conventionele of stereotactische radiotherapie, hebben we ook het effect van de bestralingen op de kwaliteit van leven na bestraling vergeleken tussen de twee studiearmen in **hoofdstuk 5.** Kwaliteit van leven werd met vragenlijsten uitgevraagd en werd beoordeeld op vier domeinen: fysiek, cognitief, emotioneel en psychologisch functioneren. Net zoals in hoofdstuk 4 zagen we veel overeenkomsten in de kwaliteit van leven scores tussen de twee studiearmen. Wel zagen we dat de scores voor fysiek

en psychosociaal functioneren beter waren in de controle arm (conventionele radiotherapie) dan in de stereotactische radiotherapie arm.

Het voorkomen van een operatie met radiotherapie

In gezond bot is er een balans tussen de afbraak en aanmaak van nieuwe botcellen. Door een botmetastase kan het zijn dat de aanmaak en afbraak uit balans raakt en er bijvoorbeeld meer botafbraak is dan botaanmaak. Hierdoor wordt de botdichtheid lager, kan het bot verzwakt raken en bestaat de kans op botbreuken. Bij wervelmetastasen is er een kans dat de metastase – door een botbreuk – neurologische uitval veroorzaakt. Een operatie is dan nodig voor herstel of om verdere uitval te voorkomen.

Radiotherapie kan ook invloed hebben op de balans tussen de botaanmaak en -afbraak. Radiotherapie kan botaanmaak stimuleren waardoor de botdichtheid, en daarmee mogelijk de mechanische sterkte, toeneemt. Het doel van **hoofdstuk 6** was om de verandering van botdichtheid te meten in wervelmetastasen na radiotherapie. Om dit te kunnen meten hebben we patiënten uit het PRESENT cohort geselecteerd waarvan een CT-scan beschikbaar was voorafgaand aan, en (maanden) na de bestraling. Op de CT-scan hebben we de botdichtheid gemeten voor en na de bestraling in de wervelmetastasen, en daarnaast in een wervel waarin geen metastase zat en buiten het bestraalde gebied lag (controlewervel). We zagen dat de botdichtheid na de bestraling toenam, en dat dit effect versterkt werd door het gebruik van botafbraak-remmende medicatie. De toename van botdichtheid door de medicatie werd ook gezien in de controlewervel, maar deze toename was minder sterk dan in het bestraalde bot, waardoor de toename in botdichtheid mogelijk inderdaad toe te schrijven is aan de radiotherapie. Verder onderzoek moet aantonen of een toegenomen botdichtheid ook betekent dat de mechanische sterkte van het bot is toegenomen. Als dat zo is, kan een operatie mogelijk worden vermeden.

Zoals eerder beschreven stijgt het aantal patiënten met botmetastasen, en hiermee ook het belang van een goede behandeling om kwaliteit van leven te waarborgen. Concluderend kan worden gesteld dat de behandeling van botmetastasen verder gepersonaliseerd moet worden, en dat tijdige evaluatie van nieuwe technieken van groot belang is. De uitkomsten van de studies in dit proefschrift dragen bij aan het personaliseren van deze behandeling om de kwaliteit van leven en zorg optimaal te houden.

List of publications

Quality of Life After Stereotactic Body Radiation Therapy Versus Conventional Radiation Therapy in Patients With Bone Metastases. Pielkenrood BJ, Gal R, Kasperts N, Verhoeff JJC, Bartels MMTJ, Seravalli E, van der Linden YM, Monninkhof EM, Verlaan JJ, van der Velden JM, Verkooijen HM. Int J Radiat Oncol Biol Phys. 2022 Apr;112(5):1203–15.

Endometrial sampling before or after saline contrast sonohysterography in women with postmenopausal bleeding (ESPRESSO Trial): A multicenter randomized controlled trial. Vroom AJ, Aerts L, Bongers MY, Lim AC, Pielkenrood BJ, Geomini PMAJ, van Hanegem N. Acta Obstet Gynecol Scand. 2021 Jan; 100(7):1258-1264.

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About the Author

Bart Pielkenrood was born in Haarlem on the 21st of May 1990. After primary school he finished secondary school in Zoetermeer after which he went to study Pharmacy in Groningen. In 2009 he enrolled in Maastricht University Medical School. In his third year he started with research on tinnitus at the ENT-department. In the last year of his master's, he went to Boston for his research internship at the department of Orthopedic Surgery of the Massachussetts General Hospital. He finished medical school with a rotation at the department of orthopedic surgery in the UMC Utrecht with prof dr. JJ Verlaan. Early 2017 he started with his PhD research on the treatment of bone metastases in the UMC Utrecht under supervision of prof. dr. Verkooijen and prof dr. Verlaan. In September that year he started with the epidemiology master with specialization tracks clinical epidemiology and medical statistics. After a year as resident not in training in pulmonary medicine at Maxima Medisch Centrum in Veldhoven, he started his training as general practitioner at Radboud University in 2021.

In his spare time, Bart enjoys to spend time with his family, play (board)games and cook. Specifically, to prepare charcuterie and to barbecue on the smoker.

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