Quality of life in painful bone metastases

Results from the Dutch Bone Metastasis Study

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General introduction and outline

Incidence

In the Netherlands, over 100.000 patients are diagnosed with cancer yearly, while more than 40.000 patients die each year because of the disease. (1) The total number of cancer patients is increasing due to, on the one hand, growth and ageing of the population with a longer life expectancy and, on the other hand, improved cancer treatments and therefore increased disease-specific survival. (2,3)

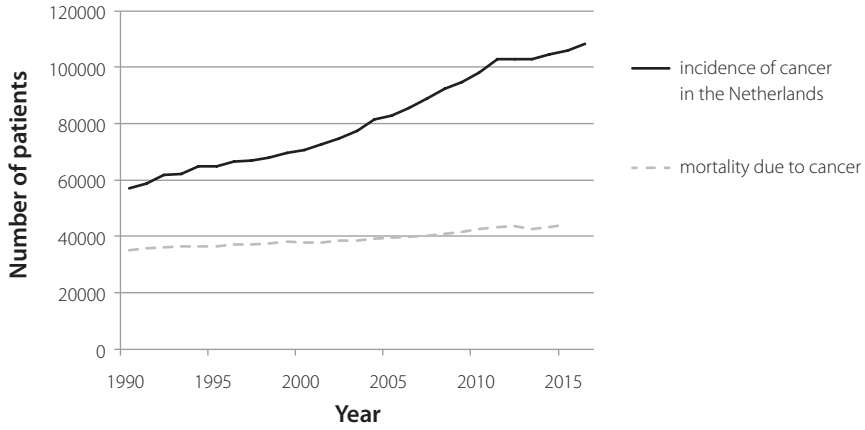

Figure 1 Incidence and mortality of cancer in the Netherlands.

Source: the Dutch Cancer Registry, IKNL© aug.2017. Printed with permission.

Bone metastases

In itself, every cancer has the potential to spread to other organs or tissues. Distant metastases arise through the lymphatic system and/or hematogeneous. Bone tissue for example, is highly vascularized and contains bone marrow, which is a fertile soil for tumor cells to seed. (4,5) Therefore, patients with cancer frequently develop bone metastases as a sign of disseminated disease. The chance of developing bone metastases depends, among many other factors, on the primary tumor type. Older studies show that breast cancer and prostate cancer metastasize to the bone frequently, with incidences up to 70%, while melanoma or bladder cancer have a lower tendency to metastasize to bone. (5-7)
Bone metastases can become symptomatic in more than 50% of patients with bone metastases from breast cancer. (8,9) Patients may experience pain or compression of the spinal cord may occur, leading to neurological deficits. Other possible sequelae are bone marrow suppression leading to anemia and thrombocytopenia, fractures of the involved

bone, leading to pain and functional problems, and hypercalcaemia, due to bone destruction, which can be life-threatening if untreated. (8-11) Patients with disease confined to the bone at the time of diagnosis of bone metastases have the highest chance of developing those events, probably due to the longer survival time compared to patients with synchronous visceral metastases. (8,12)
Pain is a common symptom in palliative cancer patients. In a large systematic review involving more than 25.000 palliative cancer patients, the reported mean prevalence of pain was 71% (13) and numbers do not seem to decrease over the years. (14,15) Bone metastases are a major source of pain.
In patients with bone metastases, the underlying mechanisms that cause pain are not completely understood. Pain is probably due to several factors, like the local destruction of the bone by the tumor, activation of the nociceptors by stretching of the periosteum and increased pressure within the bone. (5,16,17)

Quality of life and painful bone metastases

Patients with a solitary or a maximum of five metastases (in bone or elsewhere, the so-called oligometastatic disease), in a good clinical condition and a favorable primary tumor such as breast cancer, may represent a subgroup of patients, where the goal of treatment may be long-term pain control and perhaps even long-term survival. (18,19)
In the majority of patients with painful bone metastases however, multiple bone metastases and frequently also visceral metastases are present. (12,20) In those patients, the focus of treatment shifts from cure to a phase where improvement or maintaining quality of life is the main aim. The traditional oncological treatment endpoints, like prolonging survival are often less or even not appropriate. It is important for both patients and their relatives as well as their caregivers to be aware of this shift in focus.
The World Health Organization (WHO) defines palliative care as "*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." "Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy.*" (21)
In palliative care, symptom control and improving or at least maintaining quality of life (QoL) are key issues. Therefore, all decisions regarding palliative treatment of cancer should weigh the impact of side-effects on quality of life against the benefit in terms of disease control and QoL it provides for the individual patient. If patients and their treating physicians are aware of the expected course of QoL, this may help them in treatment decisions in the context of a limited survival. Based on a literature search, Murray et al. have developed a distinctive pattern of the course of QoL in patients with metastasized cancer, showing

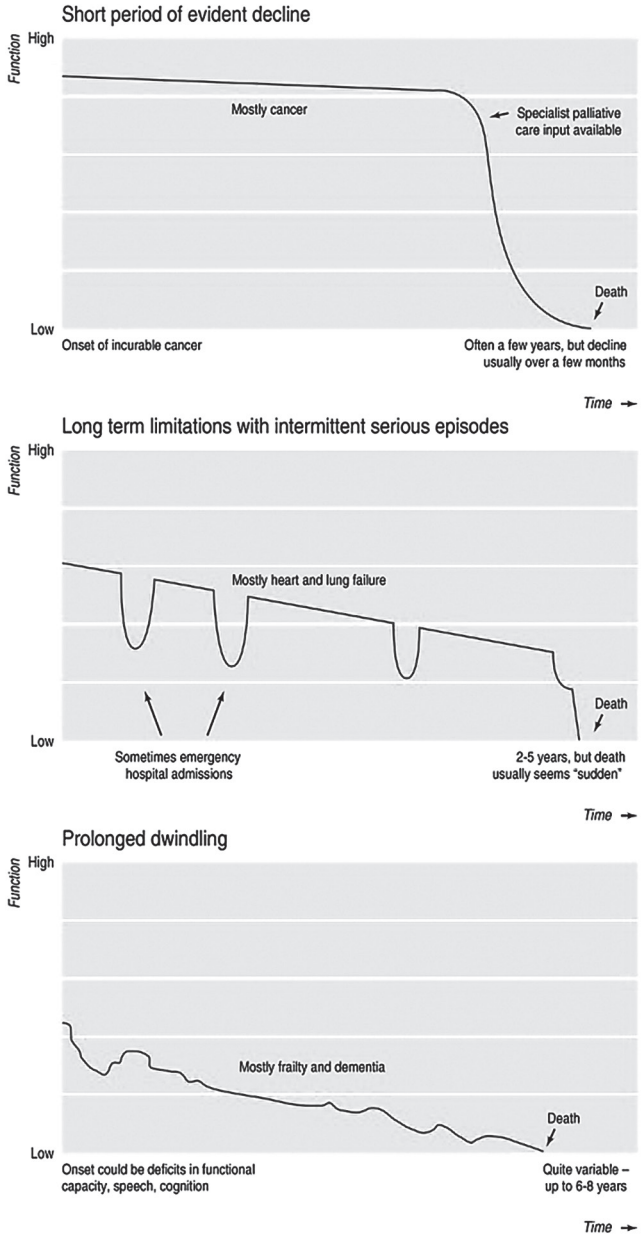

Figure 2 Typical illness trajectories for people with progressive chronic illness.

Source: Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. BMJ 2005 Apr 30;330(7498):1007-1011. Printed with permission.

a rather stable course for a long time, followed by a short and swiftly declining phase towards the end of life. This pattern is different from the course in other life-threatening diseases like chronic obstructive pulmonary disease and cardiac failure.(22)
Painful bone metastases have a negative impact on the overall QoL of patients (23,24), therefore adequate pain control is of utmost importance.

Pain management

Pain management can be achieved by a multimodality approach, depending on the needs and wishes of the individual patient, involving non-pharmacological and pharmacological treatment, psychosocial support, systemic anticancer treatment and/or local treatment like radiotherapy. (25) Initially, most patients start with pain medication only. The WHO initiated the so-called analgesic ladder, starting with non-opioids (step I). If this step provides insufficient pain relief, it was followed by weak opioids (step II) and in the last step by strong opioids (step III). (26) In oncology however, step II is frequently left out, and strong opioids are started when non-opioids provide insufficient pain relief. (27) When using strong opioids, side effects may occur, like constipation, drowsiness and nausea. (28,29) Despite pain management guidelines, treatment of pain may be inadequate, as shown in a Canadian study in which up to 48% of patients did not receive adequate pain medication for painful bone metastases. (30)

Radiotherapy

Radiotherapy is frequently used to treat painful bone metastases. In two retrospective studies including in total over 1100 patients with bone metastases from breast and non-small cell lung cancer, more than 74% of those patients received radiotherapy. (11,12) Multiple randomized controlled trials have compared different treatment schedules for this indication, varying from a single fraction to twenty fractions. (31,32)
A recent systematic review including all 25 randomized controlled trials reports an equal response rate after a single fraction compared to multiple fractions. In intention-to-treat analyses, the overall response rate was 60 and 61% respectively, with a complete response rate of 23% and 24%. When drop-out patients were excluded, the overall response rate was 72% and 74%, with a complete response rate of 28% versus 30% for single and multiple fraction treatment respectively. No significant differences were noticed in complete or overall response rates between the treatment schedules. Furthermore, no differences in toxicity between treatment schedules were observed. (31,32)

Dutch Bone Metastasis Study

The Dutch Bone Metastasis Study (DBMS) is unique compared to the other trials in terms of the amount of patients and the contents, frequency and duration of follow-up and gave already answers not only on pain response but also on several other questions concerning patients with painful bone metastases.

The DBMS is the largest randomized trial worldwide in patients with painful bone metastases. It was a nationwide, randomized trial, with 17 out of 21 radiotherapy institutions in the Netherlands participating. From March 1996 to September 1998, 1.157 patients with uncomplicated painful bone metastases from solid tumors were randomized between a single fraction of 8 Gray (Gy) or 24 Gy in six fractions. At randomization and during follow-up, patients filled out weekly questionnaires for thirteen weeks and monthly thereafter until two years of follow-up, death or closure of the study. Those questionnaires contained, among others, questions from the Rotterdam Symptom Checklist (33) on different domains of quality of life, questions about pain score, side-effects from treatment, general well-being and pain medication. (34,35)

Pain response

The main endpoint was pain response, which was initially defined as a decrease of at least two points on a scale of 0 to 10 compared to the baseline pain score. Overall, 71% of patients experienced a pain response within 3-4 weeks after treatment, with no difference between treatment arms. Toxicity and overall QoL were comparable. However, 25% of patients initially treated with a single fraction of 8 Gy were retreated, compared to 7% of patients treated with 6 fractions of 4 Gy. (35)

After the initial publication, the international consensus agreement was published in 2002 about endpoint definitions in clinical trials in bone metastases (36). Subsequently, a further analysis of the DBMS was published, using those international criteria in terms of pain response and taking into account the effect of retreatment (34). In those criteria, which were updated in 2012, a complete pain response is defined as a pain score of 0 at the treated site with no concomitant increase in analgesic intake. A partial pain response includes a pain reduction of 2 or more at the treated site on a scale of 0 to 10 without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain. (37) The re-analysis of the DBMS confirmed equal effectiveness between both treatment arms, with a pain response rate of 71% and 73% for the single fraction and the multiple fractions respectively, taking into account changes in pain medication and excluding the effect of re-irradiation. Including retreatment, the response rate for single fraction treatment increased to 75%, while the response rate of multiple fraction treatment remained unchanged. In conclusion, both single and multiple fraction treatment provided equal palliation. (34)

Cost-effectiveness

When treatment arms show comparable results, other factors like costs may play a role in the choice of treatment. In the multiple fraction arm, patients have to pay several visits to the hospital, with theoretically more costs than a single visit. However, the higher percentage of retreatment in the single fraction treatment arm may result in higher costs. In a cost-utility analysis, the total costs for both treatment arms were compared, including retreatment and non-medical costs, like travel costs or costs of domestic help. For the non-medical cost estimation, a subset of 166 patients answered additional questionnaires. It appeared that, in the Netherlands, a single fraction treatment had lower costs, both medical and societal, compared with the multiple fraction treatment. At that time, the medical costs differed almost 900 dollar, while the societal costs differed over 1700 dollars, both in favor of the single fraction regimen. This outcome, combined with the comparable pain response rates and quality of life, confirmed the conclusion that a single fraction treatment should be standard of care in patients with uncomplicated painful bone metastases.(38)

Spinal metastases

However, other treatment modalities might be also relevant in specific patients and choices between treatments have to be made. In patients with painful vertebral metastases for example, although radiotherapy is in general treatment of choice, surgery may also be a treatment option, mainly in patients with neurological complaints or vertebral instability or in situations where the limit of radiation dose to the spinal cord has been reached. When considering a major treatment like surgery, prognosis becomes more relevant. Therefore, all 342 patients included in the DBMS with painful vertebral metastases were studied and prognostic factors for survival were identified. The final scoring system contained three factors, namely Karnofsky Performance Status (39), primary tumor and the absence of visceral metastases. With those three factors, a scoring system was developed, dividing patients into three subgroups, with a median survival of 3 months (group A), 9 months (group B) and 18.7 months (group C). (40) This scoring system enables physicians to determine which patients are suitable for an invasive treatment like surgery or which patients will not likely live long enough to benefit from those treatments.

Femoral metastases

In patients with femoral metastases, surgery may also be a relevant treatment option, if fracture risk is high. It is relevant to prevent fractures and identify those patients most at risk before a fracture might arise, in order to offer the appropriate treatment, like prophylactic surgery. In the DBMS 14 fractures arose in 102 patients with in total 110 painful femoral metastases. Twenty-three percent of patients with femoral metastases experienced a fracture after a single fraction versus 7% after multiple fractions. In order to identify the factors predicting patients most at risk, the radiographs of all 102 patients

were studied. The analyses showed that fracturing of the femur mostly depended on the amount of axial cortical involvement of the metastasis and not on treatment schedule. Therefore, it was recommended that patients with metastases involving 30 mm or more of the axial cortex should be referred to discuss a prophylactic surgical procedure to prevent fracturing. When the patient is not eligible for surgical treatment, then a higher total radiation dose should be considered. (41) Furthermore, analysis showed that conventional risk factors, commonly used at the time of publication, like circumferential cortical destruction, increasing pain or radiographic osteolytic appearance, overestimated the risk of a fracture. (42) Up to date, research aiming at identifying patients most at risk for a fracture does still not show a better clinical risk factor to use, although progress is being made using computer models. (43,44)

Patients with relatively long survival

In patients with a relatively long survival, the question remained which treatment schedule should be preferred, if chances were for example that complaints would recur earlier after one of the treatment arms. In total 320 patients with a survival of one year or longer after treatment were included in the DBMS. In those patients, pain response rates were similar after both treatments: 87% after 8 Gy and 85% after 24 Gy. Duration of response and progression rates were also similar, leading to the conclusion that a single fraction of 8 Gy is also justified in patients with a favourable prognosis. (45)

On the other hand, patients with limited survival were also studied, to determine the efficacy of palliative radiotherapy for painful bone metastases in these patients. Since they might represent a different group than patients who survive longer, with a more aggressive disease and other primary tumors, their response to palliative radiotherapy might be different. (46) Furthermore, earlier analyses showed a mean time to response of three weeks (34), which might be too long for patients with a short survival to benefit. In total, in the DBMS, 274 patients died within twelve weeks after randomization, mainly patients with primary lung cancer. Using intention-to-treat analysis, 44% of patients treated with multiple fractions experienced a pain response, compared to 47% of patients treated with a single fraction. When comparing the pain response in assessable patients only, these numbers were 56% for multiple fractions and 53% for a single fraction. In both treatment groups, the median time to a pain response was two weeks. There were no differences between treatment groups in terms of progression of pain after initial response or retreatment rates. Thus, palliative radiotherapy of painful bone metastases is a valid treatment option in patients with a short survival, where a single fraction is preferred. (46)

Dose variation of single fraction radiotherapy

Some other trials studied a single fraction dose lower than 8 Gy. In 1992, a study was published comparing 8 Gy and 4 Gy in a single fraction. It showed a higher response rate, although only taking pain score into account, for the 8 Gy treatment (69% versus 44% at

4 weeks). (47) In 1998, results of a study comparing single fractions of 4 Gy, 6 Gy and 8 Gy were published. In total, 327 patients were randomized, showing overall response rates, again only taking pain scores into account, of 59%, 73% and 78% respectively. (48) Only one randomized trial studied a higher single fraction dose of conventional radiotherapy of 10 Gy, compared with 22,5Gy in 5 fractions. Overall response rates were 84% (single fraction) versus 89% (multiple fractions), with no significant difference between treatment arms. (49)
A systematic review aiming to determine the optimal dose of single fraction, shows 8 Gy to be statistically superior to a single fraction of 4 Gy. (50) This was recently confirmed by a IAEA randomized multicentre trial comparing a single fraction of 4 Gy with a single fraction of 8 Gy. In this trial, 651 patients were randomized, showing overall response rates of 88-90% versus 80-86%, depending on the instrument of pain measurement, both significantly in favor of the 8 Gy treatment.(51)

Retreatment

The duration of a pain response is also an important outcome. In the DBMS, median time to progression of pain was 24 weeks for the multiple fraction treatment and 20 weeks for the single fraction, while the median survival was 30 weeks. Mean times to progression were 19 and 18 weeks respectively. In patients surviving one year, 49% showed progression during that first year. (34,35) Therefore, in long-term survivors, retreatment is an important issue.
In several studies, despite the documented equal response rates, an increase in retreatment was noticed after a single fraction compared to multiple fractions: 20 to 21.5 percent versus 7,4 to 8 percent of patients initially treated with a multiple fraction schedule. (31,32,52) This is in line with the DBMS, where the treatment schedule seemed to be predictive of retreatment. Retreatment was given earlier after a single fraction compared to multiple fractions and at lower pain scores. This difference was contributed to the expectations of treating physicians at that time, believing that multiple fractions would be better in relieving pain. (34)
Although re-irradiation is frequently performed, data on effectiveness and recommended treatment schedule are scarce. A systematic review including 10 articles showed a re-irradiation rate of 20%, ranging from 11 to 42% between studies. In a meta-analysis, including 7 articles using different dose schedules and different definitions of a pain response, an overall pain response was achieved in 58% of patients. Complete response rates ranged from 16 to 28% and partial response rates from 28 to 45%. Because overall study quality was found to be mediocre and many clinical and methodological differences existed between studies, no recommendation could be made for re-irradiation dose and fractionation. (53) Another systematic review included 15 articles and found an overall response rate of 68%, with a 20% complete response rate and a 50% partial response rate. This review concluded that further research was needed to answer further questions, for example which fractionation schedule should be recommended. (54)

To answer this question, a large international randomized trial was undertaken, in which sixteen Dutch radiotherapy institutions participated. The goal was to study the effectiveness of re-irradiation for recurrent or non-responding pain after initial radiotherapy, studying different dose schedules for re-irradiation. In this trial, 850 patients who were previously treated with radiotherapy for painful bone metastases and were referred for retreatment, were randomized between 8 Gy in a single fraction and 20 Gy in multiple fractions. The trial showed that a single fraction was not inferior to multiple fractions and less toxic. The overall response rate in the intent-to-treat analyses was 28% for patients treated with a single fraction of 8 Gy versus 32% in patients treated with 20 Gy in multiple fractions. In the per protocol analyses these numbers were 45% versus 51% respectively. No significant differences in global QoL were noted between both treatment arms. Toxicity consisted mainly of lack of appetite and diarrhea, which were both significantly less frequent after the single fraction treatment compared to the multiple fractions: 56% versus 66% and 23% versus 31%, respectively. (55) A systematic review including these results showed overall response rates for both initial and retreatment of 71-73% in the intent-to-treat analyses and 85-87% in the assessable population, excluding the patients who dropped out. (56)

Radiotherapy – conclusions

In conclusion, for the majority of patients with uncomplicated painful bone metastases, radiotherapy provides good palliation and is the treatment of first choice. (25) Given the equal outcomes for single and multiple fractions, comparable toxicity and convenience for patients due to the reduction of hospital visits and reduced costs, a single fraction of 8 Gy is the golden standard in the treatment of uncomplicated painful bone metastases.

Remaining questions

Although the evidence for a single fraction of 8 Gy is overwhelming (31,32,55) and patients also prefer to be treated with a single fraction (57), globally, patients are still treated with a variety of treatment schedules (58,59). This choice of treatment schedule may be influenced by several factors, such as geographical location (58), prognosis, patient age, site of irradiation and experience of the treating physician (59). Patients with a poor prognosis or higher age are more often treated with a single fraction than younger patients and those with a better prognosis. (59) In this thesis, our goal is to further increase the insights in palliative radiotherapy for painful bone metastases and to help physicians determine the treatment strategy which is most appropriate for their individual patient. Therefore, we formulated the following remaining questions.

Estimation of survival

For both patients and physicians, it is important to be able to predict remaining survival of the individual patient, because it is a vital element in decision making. (60-62) An estimation of survival is important for patients and their relatives (63), to be able to handle end-of-life issues and because it impacts their choice in treatments (61,62). For the individual patient, the physician has to weigh the costs for the patient, in terms of time investment and toxicity, versus the benefit, namely the expected effectiveness, time to response and response duration. Inaccurate survival estimations may lead to inadequate treatment.

After developing bone metastases, survival is in general limited (8,20,64), but very heterogeneous. Among other factors, this heterogeneity is related to the presence of other metastases, mainly visceral, the primary tumor type, physical condition of the patient, systemic treatment options and response. (12,40,64-69)

Several studies report that health care professionals tend to overestimate remaining survival time of their patients, based on the available clinical factors and their own experience. (60,70-75) The most helpful tool to estimate survival is the Karnofsky performance status (KPS) (39), a measure of a patients' functional capacity, which has been shown to be correlated with survival. (40,45,70,73,75-80) Global quality of life scores or patient-reported pain scores may also be correlated with survival. (81,82)

Since a single score of performance status or QoL is not likely to be accurate, several prognostic models exist, trying to estimate remaining survival times using multiple variables. Those models (40,65,80,83-85) are in general time-consuming, or use variables not widely available for every patient, for example laboratory variables (83,85) or specific clinical variables like dyspnea, edema or oral intake (65,83,84).

These models are infrequently used in practice (60). Therefore, there remains a need for a simple, but valid tool to estimate remaining survival time in order to make adequate treatment decisions.

Toxicity

The physician has to weigh the impact of a palliative treatment in terms of the expected benefit and toxicity in order to make adequate treatment decisions. Side-effects from radiotherapy depend mainly on the treated location and the surrounding organs, like bowel, stomach or bladder. For treatment of the long bones for example, in general, those organs are not in proximity of the target volume, making it a treatment with little toxicity. For spinal metastases, those organs are more likely to be in the radiation field. In general, side-effects from radiotherapy of spinal metastases are mild and depend on factors like field size, dose and the anatomic area being irradiated. (34,86-88) Possible side-effects of radiotherapy of spinal metastases, experienced by 35-50% of patients, are nausea, vomiting, abdominal pain, diarrhea and skin complaints. (49,89-91) When treating painful spinal metastases, two conventional treatment techniques are frequently used, namely a single field from

posterior and two opposing fields from anterior and posterior. Both techniques have their advantages, the posterior field results in a lower dose to the anterior organs, although at the cost of suboptimal coverage of the vertebra. The advantage of the opposing fields is a better dose distribution, while sparing the posterior skin, which can be relevant when a patient will undergo spine surgery in the future. (92-95) In the literature, no prospective data on the toxicity of those treatment techniques can be found. The question remains which technique should be preferred in terms of toxicity, also taking into account the response rates of both treatment techniques. To be aware of the expected toxicity is useful for both patients and their physicians, in terms of expectations, treatment choices and possibly prophylactic measures to reduce toxicity.

Psychological distress

An important aspect of QoL is psychological distress, which is defined as a negative emotional experience that may interfere with the ability to cope effectively with the disease, its physical symptoms and treatment. (96) Symptoms like anxiety, worrying, nervousness and depression contribute to psychological distress (33) and are quite common in patients with metastasized cancer, with a prevalence of up to 50% in incurable cancer patients (13). Although nearly 50% of patients experiences psychological distress, only a small percentage is referred for intervention, mainly because distress is not recognized and because of unawareness of the treatment possibilities and the perception of not needing any help. (97,98) It would therefore be helpful to be able to identify those patients who are more prone to developing psychological distress, in order to recognize distress early and offer those patients treatment.

Quality of life in patients treated with radiotherapy for painful bone metastases

In the international consensus on bone metastases, 91% of international experts agree that quality of life instruments, preferably specifically validated for bone metastases, should be incorporated in all clinical trials. (37) Despite this recommendation, few of the aforementioned randomized trials (31,32) focus on the impact of radiotherapy on QoL or document this impact only briefly (49,99). In a systematic review (99), three randomized trials were identified reporting changes in QoL after palliative radiotherapy on bone metastases, with a maximum amount of 209 patients. Those three trials used four different QoL instruments, namely the Spitzer's index, the Hospital Anxiety and Depression Questionnaire (49), a five point global QoL-scale (89) and a measurement of net pain relief (100). In general, those trials concluded that QoL improved after palliative radiotherapy. (99) Both Gaze and Nielsen found that improvements of QoL were of similar magnitude irrespective of treatment schedule (single or multiple fractions). (49,89) The more recent retreatment study found a better QoL two months after retreatment in responders compared to non-responders. (101)

Several non-randomized trials studying radiotherapy on bone metastases report on QoL, but in most studies this is restricted to a very brief description of the impact of treatment on QoL, mostly measured at a limited amount of time points and with a variety of questionnaires, making it difficult to compare these outcomes. (99) In those articles, between 59 and 528 patients were studied. (101-105) The amount of measurements in follow-up ranges between one (101,104,105), to a maximum of five, the latest twelve weeks after treatment (102). One article documenting the compliance of patients showed only 40% of patients filled-out their questionnaire after two months. (103)
In general, those studies concluded that radiotherapy improved QoL, mainly in patients experiencing a pain response. (99,102-105) The question remains how QoL develops after palliative radiotherapy for painful bone metastases and whether patients experiencing a pain response show a better QoL than patients without a pain response. Knowing this would help both patients and their physicians in adjusting their expectations.

Influence of age on effectiveness of radiotherapy and QoL

As mentioned earlier, the number of elderly cancer patients increases due to the longer life expectancy and improvements in cancer treatments (2,3). However, the elderly population is more fragile than the younger population. With their specific age-related problems and needs, older patients are possibly more vulnerable to side-effects of treatment. Furthermore, this group of patients is frequently excluded from or under-represented in clinical trials, making it difficult to translate the results of the trials to the elderly population. (106) Several studies show that elderly cancer patients receive different treatments than younger patients (107-110), and less often palliative treatments like radiotherapy. (111-113)
The questions remains whether this difference in treatment choices is justified and whether QoL and response rates are different for elderly patients compared to younger patients. With the ongoing changes in the patient population, those questions become more relevant.

Pain flare

Shortly after treatment for painful bone metastases, a pain flare may arise, which has a negative effect on QoL. (114) A pain flare is defined as a two-point increase of the worst pain score on an 11-point rating scale, compared to baseline, without a decrease in analgesic intake, or a 25% increase in analgesic intake without a decrease in worst pain score. A pain flare is distinguished from progression because the worst pain score and analgesic intake return to baseline levels after the flare. (115)
In a review of the literature the reported incidence of a pain flare is up to 44% (116), with a median duration of 1.5 days. (117) The majority of patients who experienced a pain flare indicated to prefer the prevention of this pain flare instead of managing it with break-through medication. (114) However, prediction seems difficult. Although several factors

have been mentioned, there is no consistency in how to predict a pain flare. Its occurrence may depend on factors like primary tumor type or fractionation schedule. (117,118)
Since a pain flare is thought to be caused by edema and stretching of the periosteum, dexamethasone has been prescribed in two small studies to determine whether this would influence the incidence of a pain flare. In those two studies, the incidence of a pain flare with prophylactic dexamethasone in two different dose schedules, was 22 and 24% respectively. (119,120) Recently, a large randomized trial in almost 300 patients was published, showing a reduction in pain flare when using dexamethasone. The study randomized between a daily placebo and 8 milligrams of dexamethasone for five consecutive days, starting on the day of treatment. In total, 26% of patients in the dexamethasone group developed a pain flare, compared to 35% of patients in the placebo group (p:0.05). The authors concluded that dexamethasone is efficacious in the prophylaxis of a pain flare. Furthermore, they concluded it improved QoL by reducing nausea and increasing functional activity and appetite, without serious adverse effects. (121) These results need to be confirmed before implementing dexamethasone in daily clinical practice. Moreover, the optimal dosing schedule needs to be established.

Outline of this thesis

In this thesis, several unanswered research questions regarding patients with painful bone metastases, are addressed. For the analyses, the data of the Dutch Bone Metastasis Study (DBMS), the largest randomized radiotherapy trial in patients with painful bone metastases to date, were used. In this trial, between 1996 and 1998, 1157 patients were randomized between a single fraction of 8 Gray and six fractions of 4 Gray. The primary endpoint was pain response. The study proved equal effectiveness of both treatment schedules.
In **chapter 2** we assess the value of a simple tool to predict survival in patients with painful bone metastases, to assist both patients and physicians in making appropriate treatment decisions. Our goal was to create a model that would be simple and easy to use, to help physicians in their daily practice. Since the DBMS included patients in the late nineties and survival may have changed over the years, we validated this model externally with a more recent database.
Chapter 3 describes the effectiveness and toxicity of two different radiotherapy treatment techniques (a single posterior field versus two opposing fields from anterior and posterior), used for patients with painful spinal metastases, to determine which technique should be preferred for individual patients in terms of toxicity. Both abdominal and skin complaints were studied. We compared both treatment techniques, different levels of the spinal column and fractionation schedules. Furthermore, we relate predictors to toxicity.
Chapter 4 shows the course of psychological distress after radiotherapy for painful bone metastases. At baseline, we divided patients in groups with a high, intermediate or low level of distress and followed the course of psychological distress in these three groups. Furthermore, we created a model to help predict psychological distress, in order to be able to identify those patients most at risk and refer them in time for intervention.
In **chapter 5** we studied the course of quality of life after palliative radiotherapy in patients with painful bone metastases. We modelled the course of quality of life towards death, in order to inform both patients and physicians about the expected course of QoL. We studied the detailed course of QoL, separated into different domains, namely physical, psychosocial and functional status and general health, until a maximum of two years follow-up after treatment. We analyzed the influence of baseline and follow-up variables on the course of QoL.
Chapter 6 shows the course of QoL after radiotherapy, comparing responding and non-responding patients, aiming to determine whether a pain response is related to a better QoL after treatment. A second objective of the study was to assess the value of prognostic factors to predict a pain response after radiotherapy in patients with painful bone metastases. We created a model to predict response to palliative radiotherapy, aiming to identify those patients who were highly likely to show a response and those who were not. Since response rates differ between primary tumor type, we also focused on primary tumor.

In **chapter 7**, we studied the effect of age in patients with painful bone metastases, to determine whether age should be taken into account when making treatment decisions for the individual patient. We showed the pain response in three age cohorts to see whether there were any differences in response rate. Furthermore, we created a model to predict pain response, to be able to determine whether age would predict for a pain response after palliative radiotherapy. Thirdly, we showed the course of QoL for three different age cohorts.

The **appendix** contains the study protocol of the recent Dutch multicenter, double-blind placebo-controlled trial studying the efficacy of dexamethasone in the prevention of a pain flare, aiming to find a treatment strategy to prevent the occurrence of a pain flare. In total, 294 patients were included between January 2012 and March 2016. The database of this study is currently being updated and closed, and the results will be published soon.

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An easy tool to predict survival in patients receiving radiation therapy for painful bone metastases

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Abstract

Purpose: Patients with bone metastases have a widely varying survival. A reliable estimation of survival is needed for appropriate treatment strategies. Our goal was to assess the value of simple prognostic factors, namely patient and tumor characteristics, Karnofsky performance status (KPS) and patient-reported scores of pain and quality of life, to predict survival in patients with painful bone metastases.

Methods and materials: In the Dutch Bone Metastasis Study 1,157 patients were treated with radiation therapy for painful bone metastases. At randomization, physicians determined the KPS; patients rated general health on a visual analogue scale (VAS-gh), valuation of life on a verbal rating scale (VRS-vl) and pain intensity. To assess the predictive value of the variables, we used multivariate Cox proportional hazard analyses and C-statistics for discriminative value. Of the final model, calibration was assessed. External validation was performed on a dataset of 934 patients, treated with radiation therapy for vertebral metastases.

Results: Patients had mainly breast (39%), prostate (23%) or lung cancer (25%). After a maximum of 142 weeks follow-up, 74% of patients had died. The best predictive model included gender, primary tumor, visceral metastases, KPS, VAS-gh and VRS-vl (C-statistic 0.72, 95%CI 0.70-0.74). A reduced model, with only KPS and primary tumor, showed comparable discriminative capacity (C-statistic 0.71, 95%CI 0.69-0.72). External validation showed a C-statistic of 0.72 (95%CI 0.70-.73). Calibration of the derivation and the validation dataset showed underestimation of survival.

Conclusion: In predicting survival in patients with painful bone metastases, KPS combined with primary tumor was comparable to a more complex model. Considering the amount of variables in complex models and the additional burden on patients, the simple model is preferred for daily use. In addition, a risk table for survival is provided.

Introduction

Patients who have been diagnosed with bone metastases have a heterogeneous survival. Among other factors, this is related to primary tumor, its susceptibility to treatment and the presence of other metastases, mainly visceral. (1-3) An estimation of survival is important, because it is a vital element in decision making. (4-6) The physician relies on these estimates to decide on treatment options weighing time investment and expected toxicity versus effectiveness. Inaccurate estimations may lead to inadequate treatment decisions. In addition, it is important for patients and their relatives to be aware of the expected survival time, because it impacts their choice in treatments. (5-7)

Although some prognostic models in palliative radiation therapy exist, like the models developed by Chow, and van der Linden (1, 2, 8), these are infrequently used in practice (4). Existing models are often complicated in use and time-consuming for both doctor and patient. Physicians often rely on their own estimation of life expectancy, based on their clinical judgment. Unfortunately, it is difficult to make a correct estimation. Several studies report that health care professionals tend to overestimate survival. (4, 9-14) A performance status, like the Karnofsky performance status (KPS) (15), is a measure of a patients' functional capacity and is commonly used. Several articles show the KPS to be significantly correlated with survival. (1, 8, 9, 12, 14, 16-20) A review of prognostic tools and prediction of physicians reported that the KPS was the best tool to estimate survival in terminally ill cancer patients. (9) However, another review showed little additive value of the KPS to the physicians' clinical estimation of survival in these patients. (10) In a recent retrospective study in patients with painful bone metastases from non-small cell lung cancer, the KPS was not predictive for survival. (21) Survival estimates and performance status are mostly physician-based. A recent review suggests that patients' own ratings are better predictive tools than performance status. (22) Global quality of life scores have been shown to be correlated with survival in patients with several primary tumors in both a curative as well as a palliative setting. (22) Patient-reported pain scores may also predict survival. (22, 23)

We aimed to assess the potential value of simple prognostic factors to predict survival in patients with painful bone metastases, to assist both patients and physicians in making appropriate treatment decisions. For that purpose, we used the prospectively collected dataset of the Dutch Bone Metastasis Study (DBMS), a large cohort of patients with a variety of primary tumors. (24) The aim of this study was to assess the prognostic value of the physician-rated KPS, as well as patient-reported pain and quality of life, in patients treated with radiation therapy for painful bone metastases. Secondly, we explored which simple combination of prognostic variables was able to adequately predict survival.

Patients and methods

The DBMS was a nationwide, randomized trial in patients with painful bone metastases. From March 1996 to September 1998, 1,157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or 24 Gy in six fractions. The main endpoint was pain response. Detailed descriptions and outcomes of the study protocol have been published previously. (24) The Medical Ethics Committees of all participating institutions approved the study. All patients provided informed consent. In December 1998, survival data were retrieved from the medical records or from contacting the general practitioner.

Scales

At randomization and follow-up, questionnaires were sent weekly, filled out at home and returned using self-addressed envelopes for twelve weeks and monthly thereafter until two years of follow-up, death or closure of the study in December 1998. The questionnaires consisted of the Rotterdam Symptom Checklist (RSCL) (25), a general health scale, a pain scale and medication intake. At randomization, the treating physician rated the performance status using the KPS. Patients rated their general health on a 100 mm visual analogue scale (VAS-gh), ranging from 0 to 100: the higher the score, the better the patients' general health. One item from the RSCL is a verbal rating scale for overall valuation of life (VRS-vl), rated on a seven-point Likert-type scale, ranging from 1 (meaning the patient valuated life very high) to 7 (very low valuation of life). Pain was measured using an 11-point numeric rating scale, ranging from 0 (meaning no pain) to 10 (meaning the worst pain imaginable). A pain score of at least 2 was required to enter the study. (24)

Statistical analyses

Based on the literature and availability in clinical practice, the following patient characteristics were studied for their value in predicting survival: gender (male/female), age (dichotomized into ≤65/>65 years), primary tumor (breast, prostate, lung and other), visceral metastases (yes/no) and baseline scores for KPS (categorized into 20-60, 70-80, 90-100), VAS-gh (0-33, 34-66, 67-100), VRS-vl (1-3, 4, 5-7) and pain score (2-5, 6-7, 8-10). KPS, VAS-gh, VRS-vl and pain score were clustered into subgroups to create categorical data with a sufficient amount of patients per subgroup. Gender, age, primary tumor and presence of visceral metastases were documented in all patients at study entry. The KPS, VAS-gh, VRS-vl and pain score at baseline were available for 99%, 92%, 94% and 99% of patients, respectively. We used single imputation to insert missing values. We only used the baseline measurement of these variables in order to be able to predict survival before treatment. Pearson's correlation coefficients were assessed in order to assess the risk of multicollinearity of the potential predictors. Survival curves were estimated and assessed using the Kaplan Meier method and the log-rank test.

Univariate and multivariable Cox proportional hazard models were applied to relate candidate predictors to survival. For the development of the predictive model, we started with all candidate predictors (full model: gender, age, primary tumor, visceral metastases, KPS, VAS-gh, VRS-vl, pain score). Subsequently we eliminated the variables by backward selection. A threshold p-value of 0.20 was chosen to limit the loss of information and to also select weaker predictors. (26) Discriminative ability of the predictive models was assessed with the C-statistic. The C-statistic estimates the probability of concordance between predicted and observed responses. (27) A C-statistic ranges between 0.5 and 1.0, where a value of 0.5 means the model is no better than chance, while a value of 1.0 means perfect discrimination. By the use of bootstrapping, the shrinkage factor and optimism were calculated and used to correct the C-statistic. To assess the overall fit, the proportional hazards assumption and the Schoenfeld residuals were checked. A calibration plot was made to visualize the predictive accuracy of the model at 3, 6 and 9 months of follow-up. (27) For external validation of the final model (28), a retrospectively collected dataset was used, including 980 consecutive patients, receiving radiation therapy for vertebral metastases between 2001 and 2010 in one hospital in the Netherlands. (29) Data on survival were retrieved from the medical records or from contacting the general practitioner. In this dataset, KPS at baseline was missing for 46 (4,7%) patients. Therefore, we used the data of the 934 patients with complete data.
The effect of variables on survival was expressed as Hazard Ratio's (HR) with 95% Confidence Intervals (95% CI). The dataset was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA). C-statistics were calculated in the R language environment for statistical computing, version 2.10 (freely available at http://cran.r-project.org).

Results

In total, 1,157 patients were included into the DBMS (derivation dataset). Mean age was 65 years (range 32-89). Fifty-four percent of patients was male. Most patients had breast (39%), prostate (23%) or lung cancer (25%). The remaining 152 patients had a variety of primary tumors, mostly bladder, colorectal or esophageal cancer. Visceral metastases were documented in 28% of patients. At baseline, mean scores (and ranges) for KPS, VAS-gh, VRS-vl and pain score were 70 (20-100), 46 (0-98), 4 (1-7) and 6 (2-10), respectively.

Survival data in derivation dataset

The median and mean survivals of the entire group were 30 and 49 weeks respectively, with a range of 0.3-142 weeks. At closure of the study, with a maximum follow-up of 2.7 years, 860 (74%) patients had died. Figure 1 shows the survival of patients by categorized KPS, VAS-gh, VRS-vl and pain score. Table 1 shows that survival differed significantly between categories of different baseline variables (gender, age, primary tumor, visceral metastases,

KPS, VAS-gh, VRS-vl, pain score), but not between the treatment arms. There was no significant difference in survival between patients irradiated for vertebral metastases and patients irradiated for bone metastases elsewhere (data not shown).

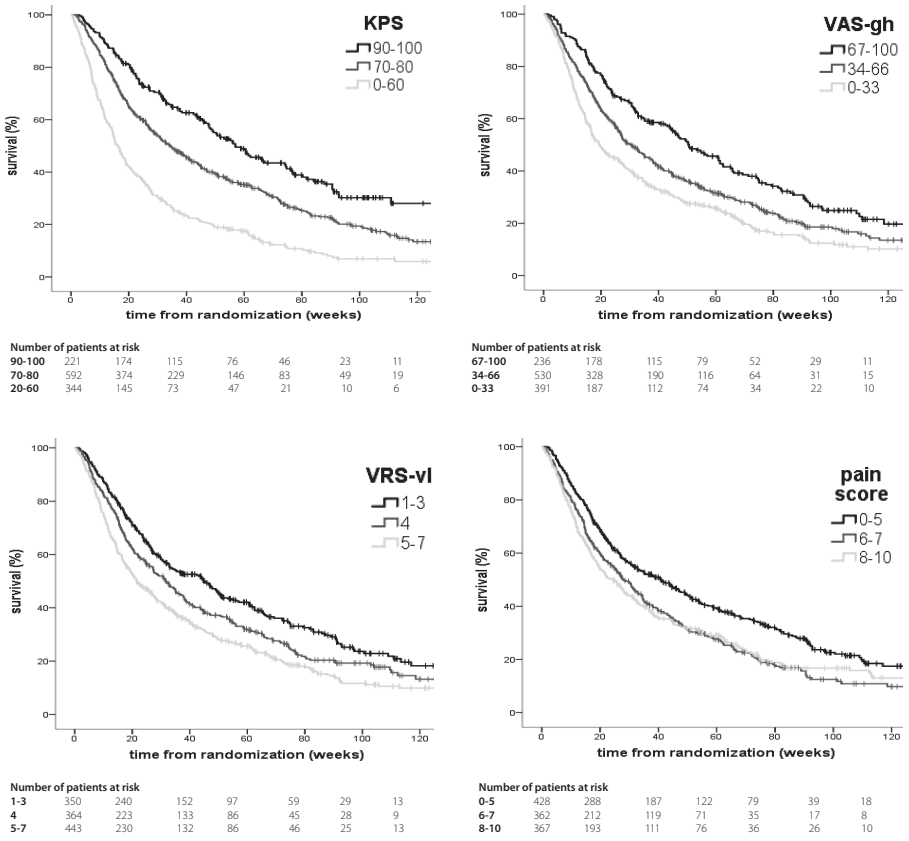


Figure 1 Survival by categorized baseline variables: Karnofsky performance status (KPS), visual analogue scoring of general health (VAS-gh), verbally rated scoring of overall valuation of life (VRS-vl), pain score.

Table 1 Survival of patients by the different categorized baseline variables.

baseline variables	*n*	*survival (weeks)*		*p-value **	*in case of >2 groups: difference between #*
		median	**range**		
gender				<0.001	
male	624 (54%)	20.7	0.3-135.6		
female	533 (46%)	49.9	0.6-142.0		
Age				0.021	
≤ 65 years	565 (49%)	34.6	1.0-141.0		
> 65 years	592 (51%)	27.4	0.3-142.0		
primary tumor				< 0.001	
breast	451 (39%)	68.7	1.1-142.0		breast-prostate (p < 0.001)
prostate	267 (23%)	39.7	1.4-135.6		breast-lung (p < 0.001)
Lung	287 (25%)	13.3	0.3-102.6		breast-other (p < 0.001)
other	152 (13%)	16.4	0.6-127.0		prostate-lung (p < 0.001)
					prostate-other (p < 0.001)
visceral metastases				<0.001	
No	838 (72%)	35.0	0.3-142.0		
Yes	319 (28%)	19.4	0.9-138.0		
treatment arm				n.s.	
1x8 Gray	578 (50%)	32.9	0.7-142.0		
6x4 Gray	579 (50%)	28.1	0.3-141.0		
KPS				< 0.001	
90-100	221 (19%)	57.0	3.0-138.0		90-100 vs 70-80 (p < 0.001)
70-80	592 (51%)	34.6	1.7-142.0		90-100 vs 0-60 (p < 0.001)
20-60	344 (30%)	16.3	0.3-141.0		70-80 vs 0-60 (p < 0.001)
VAS-gh				< 0.001	
67-100	236 (20%)	50.6	1.7-141.0		67-100 vs 34-66 (p < 0.001)
34-66	530 (46%)	30.6	0.6-138.0		67-100 vs 0-33 (p < 0.001)
0-33	391 (34%)	19.4	0.3-142.0		34-66 vs 0-33 (p < 0.001)
VRS-vl				< 0.001	
1 – 3	350 (30%)	45.1	1.4-142.0		1-3 vs 4 (p = 0.007)
4	364 (31%)	31.7	1.0-135.6		1-3 vs 5-7 (p < 0.001)
5 – 7	443 (38%)	21.6	0.3-141.0		4 vs 5-7 (p = 0.004)
pain score				< 0.001	
2 – 5	428 (37%)	40.9	2.0-135.9		2-5 vs 6-7 (p < 0.001)
6 – 7	362 (31%)	27.9	0.6-141.0		2-5 vs 8-10 (p < 0.001)
8 - 10	367 (32%)	24.4	0.3-142.0		

*: log-rank test, #: the non-significant differences are not shown, n.s.: not significant, KPS: Karnofsky performance status, VAS-gh: visual analogue score of general health, VRS-vl: overall valuation of life. KPS, VAS-gh: the higher the score, the better the well-being. VRS-vl, pain score: the lower the score, the better the well-being

Predictors for survival

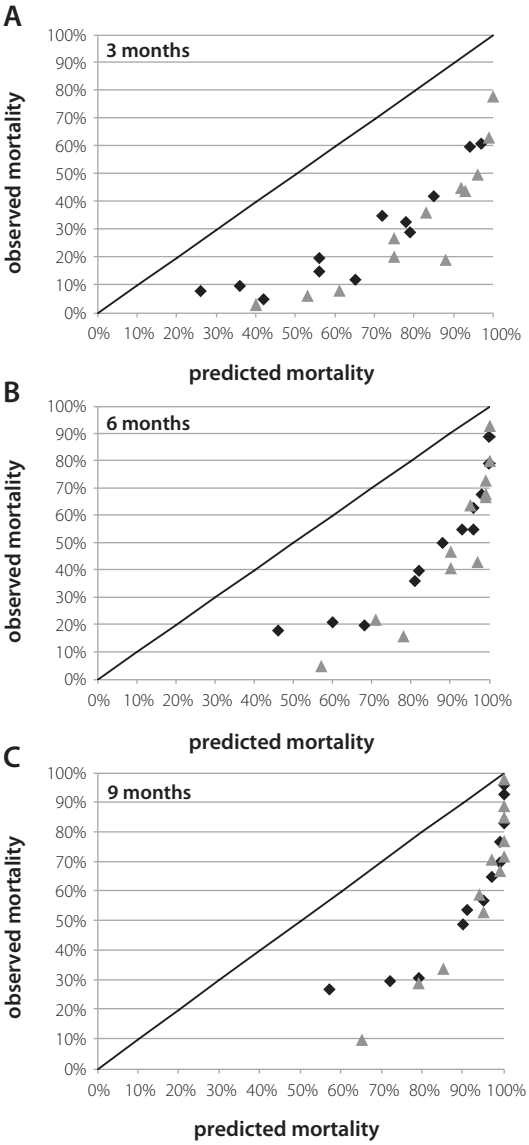
Univariate analysis showed that being male, being older than 65 years, having any primary tumor other than breast cancer, having visceral metastases, lower KPS, lower VAS-gh, higher VRS-vl and higher pain score were associated with a higher risk of death (Table 2). Next, we combined all relevant variables to investigate which combination would be most predictive for survival. In multivariate analysis (table 2), pain score did not contribute to the prediction of survival. The best predictive model included gender, primary tumor, visceral metastases, KPS, VAS-gh and VRS-vl, with a C-statistic of 0.72 (95% CI 0.70-0.74). A simplified model with only KPS and primary tumor, led to a comparable discriminative ability (C-statistic 0.71, 95% CI 0.69-0.72). Reduced models combining primary tumor with patient-rated variables VAS-gh or VRS-vl had worse predictive accuracy, with a C-statistic for both models of 0.69. Figure 2 shows the calibration plot of the reduced model. It shows estimations are overly pessimistic. In general, it predicts best in patients with lung cancer or with other primary tumors and a poor clinical condition. Table 3 shows the observed survival at three to eighteen months after treatment as a tool to use for physicians when consulting patients with painful bone metastases.

External validation

The external dataset included 934 patients with a mean age of 65 years (range 33-95 years). Fifty-two percent of patients was male and in 36% of patients visceral metastases were documented. Most patients had breast (29%), prostate (21%) or lung cancer (25%). These characteristics were the same in the full dataset. At the start of treatment, mean KPS was 70 (range 30-100).

Survival data in validation dataset

At the time of data collection, with a maximum follow-up of 11.4 years, 95% of patients had died. Median and mean survival was 21 and 60 weeks, with a range of 0.1-594 weeks. For all primary tumor sites, survival differed significantly ($p<0.001$) between the KPS groups. Table 3 shows the median survival and observed survival in the different groups of patients by KPS and primary tumor. Some patient groups have a markedly better survival in the more recent dataset compared to the DBMS dataset. In the DBMS era 58% of patients with breast cancer and a KPS of 90-100 survived 18 months, versus 75% in the validation dataset. The difference is also noticeable in patients with prostate cancer and a KPS of 90-100, where 18 months survival in the DBMS and validation dataset was 30% and 56% respectively. In lung and other primary tumors this difference is less marked. The C-statistic of our simple model, using KPS and primary tumor, was 0.72 (95%CI 0.70-0.73). The calibration plot of the model for the external validation set was almost identical to the plot for the DBMS dataset (figure 2).



Predicted versus observed mortality at:
A. 3 months
B. 6 months
C. 9 months

The solid line represents perfect accuracy of the model
◆ Dutch Bone Metastasis Study-database
▲ Validation database

Figure 2 Calibration plot of the predicted mortality at 3, 6 and 9 months after randomization versus the observed mortality in the studied patients. (**A**) 3, (**B**) 6 and (**C**) 9 months.

Table 2 Univariate (UVA) and final multivariate (MVA) Cox regression analyses on potential baseline predictors for mortality after palliative radiation therapy for painful bone metastases.

baseline variables	*hazard ratio (95% CI)*	
	UVA*	**Final MVA***
gender		
male	1.00	1.00
female	0.47 (0.41-0.54)	0.75 (0.58-0.97)
age		
≤ 65 years	1.00	#
> 65 years	1.17 (1.02-1.34)	
primary tumor		
breast	1.00	1.00
prostate	1.68 (1.40-2.02)	1.64 (1.19-2.25)
lung	4.27 (3.57-5.11)	3.67 (2.76-4.89)
other	3.49 (2.82-4.32)	2.86 (2.17-3.77)
visceral metastases		
no	1.00	1.00
yes	1.53 (1.32-1.76)	1.66 (1.42-1.94)
KPS		
90-100	1.00	1.00
70-80	1.51 (1.24-1.84)	1.37 (1.12-1.68)
20-60	2.77 (2.25-3.41)	2.39 (1.91-2.98)
VAS-gh		
67-100	1.00	1.00
34-66	1.38 (1.15-1.67)	1.17 (0.95-1.43)
0-33	1.81 (1.49-2.19)	1.35 (1.07-1.71)
VRS-vl		
1 - 3	1.00	1.00
4	1.27 (1.06-1.51)	1.07 (0.88-1.29)
5 - 7	1.60 (1.35-1.89)	1.27 (1.04-1.55)
pain score		
2 - 5	1.00	#
6 - 7	1.37 (1.17-1.62)	
8 - 10	1.39 (1.18-1.64)	

95% CI: 95% confidence interval, UVA: univariate analysis, MVA: multivariate analysis,
*: Cox regression analysis
#: did not remain in the final model, KPS: Karnofsky performance status, VAS-gh: visual analogue score of general health, VRS-vl: overall valuation of life. KPS, VAS-gh: the higher the score, the better the well-being;
VRS-vl, pain score: the lower the score, the better the well-being of patients

Table 3 Observed survival per primary tumor in patients with painful bone metastases in both the derivation dataset and the validation dataset.

primary tumor	*KPS*	*n*	*median survival*	*percentage patients with observed survival*				
			(months)	3 months	6 months	9 months	12 months	18 months
		D / V	*D / V*	*D / V*	*D / V*	*D / V*	*D / V*	*D / V*
breast		*451 / 271*						
	90-100	22% / 23%	20.8 / 39.7	92 / 97	82 / 95	73 / 91	62 / 87	58 / 75
	70-80	51% / 52%	16.8 / 19.9	90 / 94	79 / 78	70 / 71	62 / 62	46 / 54
	20-60	27% / 24%	8.1 / 7.8	80 / 73	60 / 53	46 / 47	40 / 42	28 / 33
prostate		*267 / 200*						
	90-100	25% / 13%	13.9 / 19.8	95 / 92	80 / 84	69 / 76	59 / 72	30 / 56
	70-80	54% / 49%	9.1 / 7.8	85 / 80	64 / 59	51 / 41	39 / 30	24 / 23
	20-60	21% / 40%	5.6 / 4.0	67 / 55	45 / 32	30 / 28	17 / 18	2 / 10
lung		*287 / 230*						
	90-100	14% / 9%	4.7 / 7.4	65 / 81	45 / 57	35 / 33	29 / 24	16 / 0
	70-80	47% / 41%	3.6 / 2.9	58 / 50	32 / 27	17 / 15	12 / 10	6 / 5
	20-60	39% / 50%	2.0 / 1.3	39 / 21	11 / 8	4 / 2	4 / 1	0 / 0
other		*152 / 231*						
	90-100	11% / 12%	7.2 / 3.6	88 / 64	50 / 36	43 / 29	35 / 25	16 / 21
	70-80	54% / 41%	4.5 / 3.5	71 / 55	37 / 33	23 / 23	15 / 16	7 / 10
	20-60	35% / 47%	2.4 / 2.1	40 / 35	21 / 19	7 / 11	5 / 7	0 / 2

KPS: Karnofsky performance status, D: derivation dataset (Dutch Bone Metastasis Study), V: external validation dataset

Discussion

To our knowledge, this is the first study that assessed the prognostic value of simple patient-reported outcomes and physician-based KPS to estimate survival in a large cohort of patients with painful bone metastases from a wide variety of primary tumors. Our best model with acceptable discrimination includes gender, primary tumor, visceral metastases, KPS, VAS-gh and VRS-vl. A simple model including only KPS and primary tumor showed comparable discrimination. We performed an external validation (28) in a large, more recent cohort of patients with vertebral metastases, and were able to confirm the initial results. Calibration of the model showed substantial underestimation of the actual survival of the patients in both the derivation and the validation dataset. Therefore, the model should be handled with caution. Generally, physicians tend to overestimate survival of their patients. We have no clear explanation why our model underestimates. Looking at the calibration plots per primary tumor (data not shown), our model predicted survival best in the worst prognostic groups, e.g. patients with lung cancer or with other primary tumors and a poor clinical condition. These patients were closest to their deaths. The KPS is relatively stable until the last weeks of life, when patients experience a rapid decline in performance status. (30) These are the patients in whom physicians are particularly interested to determine whether their remaining life would be too short for them to benefit from anticancer treatment. Therefore, our model functions best in patients for whom a correct estimation of survival is most relevant. Our survival table enables physicians to make an estimation of survival in patients referred for radiation therapy for painful bone metastases, based on primary tumor site and KPS. This is clearly helpful for daily clinical practice. It shows differences in survival between our dataset and the validation dataset. This may partly be due to the markedly longer follow-up times in the validation dataset, with a maximum of 11.4 years, versus a maximum of 2.7 years in the derivation dataset. Furthermore, the patients in the validation dataset all had vertebral metastases, which may be associated with a longer survival time. This does not explain the difference, as analysis of the DBMS showed no difference in survival between patients with vertebral metastases and patients with other bone metastases. Another explanation might be that patients referred after 2000 were in a better clinical condition. Our survival table shows, however, that patients in the validation dataset were generally even in a slightly worse clinical condition than the patients in the DBMS. Therefore, the differences in survival between our dataset and the validation dataset probably mostly reflect the changes in the effectiveness of systemic therapy over time, as it concerns mainly patients with breast or prostate cancer in a good clinical condition.

Several other papers identified patient-reported factors predictive for survival in patients with advanced cancer. (14, 16, 31) Our study confirms this finding, but also observed that those patient-reported factors were inferior to physician-reported KPS. A review by Gotay et al., including also studies in non-metastatic cancer patients, concluded that patient-re-

ported outcomes were often better in predicting survival than performance status. (22) They showed that in some studies performance status lost explanatory value after entering a patient-reported outcome into the model. This is in contradiction with our results, but might be explained by the different patient population. Other, smaller sized, studies in patients with metastatic cancer reported results similar to our study. Collette et al. showed in 391 patients with metastases from prostate cancer that patient-related symptoms were predictive for survival, but did not improve the predictive accuracy of several clinical variables, like performance status. (32) Efficace et al. studied 391 patients with advanced non-small-cell lung cancer and 219 patients with metastatic breast cancer. In the final models, patient-reported quality of life lost significance, while physician-rated performance status remained predictive for survival. (23, 33)

In the past, several prognostic models using a combination of variables have been developed to predict prognosis and to aid physicians and patients in choosing treatment strategies, like the palliative prognostic score (34), palliative prognostic index (35) and the predictive models developed by Chow (2, 8), Gwilliam (36) and van der Linden (1). A survey among radiation oncologists showed that prognostic models are infrequently used in practice, while the KPS was frequently used. (4) These models contain many variables and some even use laboratory findings (34, 36), with the consequence of not being usable when one of these variables is missing. Because of the time these models consume, the amount of variables, the complexity and the additional burden on both patients and physicians, we consider these models not applicable for use in daily practice. Our own group developed a model, using a subset of patients with spinal metastases, including KPS, primary tumor and visceral metastases. (1) When comparing this model and their initial model (2), Chow concludes the DBMS-model to be easier to administer at the clinic. (37) This stresses the need for a simple model. The C-statistic of the more complex model by Chow et al. is comparable to our C-statistic, although they used six variables and no correction for optimism was performed. (2) Other models showed C-statistics between 0.63 and 0.69. (8, 29, 36) All models, except the models from Chow (2, 8), did not meet current standards of methodology. (1, 34-36)

Our study is based on a unique and large cohort of patients with bone metastases from the Netherlands. Our data originate from the late nineties, which may be considered a limitation of our analyses due to possible changes in patients and treatments. Therefore, we validated our model in a recent Dutch dataset showing identical results, which makes the model applicable to current patients with painful bone metastases. Although these patients were all treated for vertebral metastases, the predictive performance in both datasets is comparable, which is the most important. (38) Moreover, 65% of the patients in the validation dataset had extraspinal bone metastases when entering the database. (29) In the DBMS, 58% of patients had other bone metastases when entering the study. Furthermore, analysis of the DBMS showed no differences in KPS or primary tumor between patients with vertebral or other bone metastases. Obviously, there has been a

selection of patients in both the DBMS and the validation dataset, because patients in progressively declining conditions will in general not be referred for pain treatment. Thus, our results apply only for those patients with painful bone metastases who are deemed fit for radiation therapy.

Conclusions

When predicting survival in patients with painful bone metastases, KPS combined with primary tumor has a similar predictive value compared to our best, more complex model, with reasonable discriminative ability. Using patient-rated variables instead of KPS did not increase the predictive value. Considering the amount of variables in the best, complex model and the extra burden on patients, the simple model is preferred for daily practice, despite underestimation of survival. In addition, a risk table for survival in these patients, based on primary tumor and KPS, is provided to assist both physicians and their patients with painful bone metastases when deciding on treatment (Table 3).

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3

Effectiveness and toxicity of conventional radiotherapy treatment for painful spinal metastases: a detailed course of side effects after opposing fields versus a single posterior field technique

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Abstract

Background: Conventional radiotherapy for painful spinal metastases can be delivered with a single posterior-anterior (PA) or two opposed anterior-posterior fields (APPA). We studied the effectiveness and toxicity of both techniques and studied whether treatment technique was predictive for abdominal and skin toxicity.

Patients and methods: Within the Dutch Bone Metastasis Study, 343 patients received 8 Gray in a single fraction or 24 Gray in six fractions for painful spinal metastases. Treatment technique was not randomized. At baseline and weekly during follow-up, patients reported pain and other physical complaints. Any complaint increasing within four weeks after treatment was noted as a side-effect. Pain response was calculated according to international standards, taking into account changes in pain score and medication. Repeated measurement analyses and multivariate logistic analyses were performed.

Results: Patients were mainly treated on the thoracic (34%) and lumbar (53%) spine and 73% received a PA-field. Pain response was similar between both techniques (74%). In patients treated at the thoraco-lumbar and lumbar spine, with multiple fractions, significantly more abdominal complaints were noticed. In multivariate analysis, radiotherapy technique did not predict for side effects.

Conclusion: Conventional radiotherapy of painful spinal metastases provides limited toxicity. Radiotherapy technique is not an independent predictor of abdominal and skin toxicity of irradiation.

Introduction

For patients with painful bone metastases, radiotherapy is an effective treatment, with a pain response rate of more than 60%. The golden standard is to treat these patients with a single fraction of 8 Gray (Gy) [1-3], aiming at pain relief with minimal toxicity.
In general, side effects from this treatment are mild and depend on factors like dose, field size and the anatomic area being irradiated. [1, 4-6] In several studies in patients treated with radiotherapy for painful bone metastases, toxicity rates between 35 and 46% are reported, consisting mainly of nausea and/or vomiting. [7-9] A recent study in 32 patients treated for painful bone metastases showed that over 50% of patients had complaints of nausea and/or vomiting, despite receiving prophylactic anti-emetic treatment. [10]
Radiotherapy to spinal metastases can be delivered with different treatment techniques. Highly conformal treatment techniques like intensity modulated radiotherapy (IMRT) and volumetric arc radiotherapy (VMAT) are used more and more, often to higher doses. Still, frequently used conventional techniques are a single posterior-anterior (PA) field or two parallel opposed fields from anterior and posterior (APPA). The advantage of a PA-field is the sparing of anterior organs like the bowel, although the coverage of the vertebrae might be suboptimal. [11] By using a PA-field, the dose to the posterior skin and paraspinal musculature can be high, which can be a problem for future surgical interventions. [12-14] The advantage of the APPA-technique is a better coverage of the vertebrae [11], while sparing the posterior skin and paraspinal musculature. A disadvantage is the higher dose in the anterior organs, possibly leading to more abdominal side effects. In the literature, however, no prospective data on the toxicity of both techniques have been published.
The aim of the present analysis is to study the differences in effectiveness and toxicity of PA and APPA techniques for the irradiation of painful spinal metastases and to identify factors predictive for side effects of treatment. We studied patients who received radiotherapy for painful spinal metastases within the randomized Dutch Bone Metastasis Study (DBMS). [1]

Patients and Methods

Details of the patient population and study protocol of the DBMS were published elsewhere. [1, 15] In summary, the DBMS was a nationwide, randomized trial in patients with uncomplicated painful bone metastases. Between 1996 and 1998, a total of 1.157 patients with painful bone metastases were randomized between a single fraction (SF) of 8 Gy or 24 Gy in six fractions. The study showed equal effectiveness of a SF versus multiple fractions (MF) with regard to pain response, which was the primary endpoint. All patients provided informed consent and the Medical Ethics Committees of participating institutions approved the study.

Patients

Patients with metastases in the cervical spine were excluded from the DBMS. [1, 15] In total, 348 patients were treated for painful metastases in the thoracic, lumbar or sacral spine. Data on spinal location and treatment technique were available in 343 patients (99%). For spinal location, the treated level of the spine (i.e. thoracic, lumbar or sacral) was registered, without specification of the specific vertebra or vertebrae irradiated. Treatment was performed with conventional treatment techniques, using either a PA-field, or APPA-fields contributing each 50% of the total dose, no other techniques were used. The prescription depth for PA-fields was typically at 4 to 6 cm, depending on the depth of the vertebra. The choice for treatment technique was left to the decision of the treating radiation oncologist, and was mostly dependent on institutional policy.

Questionnaires

At randomization and during follow-up, patients filled out thirteen weekly questionnaires and monthly afterwards until two years of follow-up, death or closure of the study in December 1998. The questionnaires consisted, among others, of the Rotterdam Symptom Checklist (RSCL) [16], a pain scale, pain medication intake and questions about itching and painful skin. No data were available on the use of anti-emetics or anti-diarrhea medication. The following items were studied to determine toxicity: diarrhea, abdominal pain, nausea and vomiting. These scores were grouped into the variable 'abdominal complaints'. Itching and painful skin were grouped into the variable 'skin complaints'. All items were rated on a four-point Likert-type scale, ranging from 1 (no complaints) to 4 (severe complaints). To facilitate interpretation, all sum scores were standardized to the range of 0 (no complaints) to 10 (severe complaints). Besides sum scores, the individual item scores were also studied. As radiotherapy of the lower spine is more likely to affect the bowel, we studied the individual abdominal items for the treated thoraco-lumbar, lumbar and lumbo-sacral vertebrae separately. Pain was measured using an 11-point numeric rating scale, ranging from 0 (no pain) to 10 (the worst pain imaginable). A pain score of at least 2 was required to enter the study. [1]

Statistical analyses

Pain response was calculated according to international criteria, taking into account changes in pain medication and pain score. [17] No fixed time interval from the date of randomization was applied. A response was calculated if at least two successive follow-up pain scores were available, which was possible in 325 patients (95%).

To compare the categorical variables at baseline, Chi-Square tests were used. To visualize and compare the course of side effects over time, we used repeated measurement analyses (mixed procedure), a longitudinal data analysis technique. Analyses were also performed adjusted for treatment institute to take into account potential confounding by indication by institutional choice for treatment technique. P-values are based on 2-sided

tests and considered significant if $p<0.05$. Figures were created based on the least square means of the repeated measurements.
To assess which baseline variables were predictive for toxicity, the complaints variable was dichotomized into having or not having complaints. For that purpose, we compared the maximal complaint scores one to four weeks after treatment with the baseline scores. If a score was higher than the baseline score, the patient was considered as having side effects of radiotherapy. The time period of four weeks was chosen because by then most side effects would be present.
We applied multivariate logistic regression analyses to relate candidate predictors to toxicity. First, we started with a full model, including all preselected variables. Subsequently, we eliminated the variables by a backward selection process with a threshold p-value of 0.20, based on likelihood-ratio test results. The chosen p-value of 0.20 intends to limit the loss of information and to select also weaker predictors, although at the cost of including 'noise' variables. [18] The preselected baseline variables, based on the literature and clinical experience, were primary tumor (breast, prostate, lung or other cancer), age (≤65 years or >65 years), gender (male or female), Karnofsky performance status (KPS) [19] (≤ 60, 70-80 or 90-100), pain score (2-4, 5-7 or 8-10), presence of visceral metastases (yes or no), concomitant systemic therapy (yes or no), treatment arm (1 x 8 Gy or 6 x 4 Gy), opioids (yes or no), spinal localization (thoracic, thoraco-lumbar, lumbar or lumbo-sacral spine) and treatment technique (PA or APPA).
The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc, Cary, NC, USA).

Results

Baseline characteristics

In general, patients with spinal metastases did not differ from the entire population of 1.157 patients with bone metastases. Table 1 shows baseline characteristics of the study population (n:343). Primary tumors were mainly breast (42%), prostate (24%) and lung (20%) cancer. The mean age was 65 years (range 32-89 years) and 52% was male. The majority of patients was in good to moderate condition, 71% had a KPS of 70 or higher. The mean pain score at baseline was 6.4 (range 2-10). Visceral metastases were documented in 28% of patients; 55% of patients received concomitant systemic therapy at the time of randomization.
250 patients (73%) were treated with a single PA-field and 93 patients (27%) with an APPA-technique. The most frequently treated localization was the lumbar spine (53%), followed by the thoracic spine (34%). The remaining patients were treated at overlapping regions. Baseline characteristics did not differ between both treatment technique groups, except for systemic therapy. More patients in the group treated with a PA-field were treated with systemic therapy (59%), compared to patients treated with an APPA-technique (43%, $p=0.009$).

Table 1 Baseline characteristics of patients with painful spinal metastases, treated with a PA or an APPA technique.

	entire cohort	*spinal patients*	*PA*	*APPA*	*difference PA vs APPA **
n	1157	343	250	93	
primary tumor					n.s.
breast cancer	451 (39%)	145 (42%)	110 (44%)	35 (38%)	
prostate cancer	267 (23%)	83 (24%)	63 (25%)	20 (22%)	
lung cancer	287 (25%)	68 (20%)	48 (19%)	20 (22%)	
Other	152 (13%)	47 (14%)	29 (12%)	18 (19%)	
Age					n.s.
≤ 65 years	565 (49%)	167 (49%)	120 (48%)	47 (51%)	
> 65 years	592 (51%)	176 (51%)	130 (52%)	46 (50%)	
Gender					n.s.
Male	624 (54%)	178 (52%)	125 (50%)	53 (57%)	
Female	533 (46%)	165 (48%)	125 (50%)	40 (43%)	
KPS					n.s.
90 – 100	221 (19%)	67 (20%)	47 (19%)	20 (22%)	
70 – 80	587 (51%)	176 (51%)	132 (53%)	44 (47%)	
20 – 60	343 (30%)	100 (29%)	71 (28%)	29 (31%)	
pain score					n.s.
2 – 4	234 (20%)	71 (21%)	54 (22%)	17 (18%)	
5 – 7	550 (48%)	155 (45%)	116 (46%)	39 (42%)	
8 – 10	366 (32%)	117 (34%)	80 (32%)	37 (40%)	
visceral metastases					n.s.
No	838 (72%)	247 (72%)	178 (71%)	69 (74%)	
Yes	319 (28%)	96 (28%)	72 (29%)	24 (26%)	
systemic therapy					0.009
No	531 (46%)	156 (46%)	103 (41%)	53 (57%)	
Yes	626 (54%)	187 (55%)	147 (59%)	40 (43%)	
treatment schedule					n.s.
1 x 8 Gy	578 (50%)	171 (50%)	129 (52%)	42 (45%)	
6 x 4 Gy	579 (50%)	172 (50%)	121 (48%)	51 (55%)	
pain medication					n.s.
no opioids	667 (58%)	170 (50%)	123 (49%)	47 (51%)	
Opioids	490 (42%)	173 (50%)	127 (51%)	46 (50%)	
spinal localisation					n.s.
thoracic spine		117 (34%)	90 (36%)	27 (29%)	
thoraco-lumbar spine		32 (9%)	27 (11%)	5 (5%)	
lumbar spine		183 (53%)	124 (50%)	59 (63%)	
lumbo-sacral spine		11 (3%)	9 (4%)	2 (2%)	

PA: posterior-anterior field, APPA: anterior-posterior and posterior-anterior field
KPS: Karnofsky performance score; Gy: Gray; n.s.: not significant; *: Chi-Square

At baseline, the mean scores of the individual complaints items were low, varying from 1 (no complaints) to 2 (minor complaints), on a scale from 1 to 4. The mean sum score of abdominal complaints was 1.3 (range 0-7.5, on a scale from 0 to 10) and the mean sum score of skin complaints was 0.7 (range 0-8.3, on a scale from 0 to 10). No baseline differences in items or sum scores between the two treatment groups were observed.
A preference per treatment institute was noticed for treatment technique. Institute policy and preferences mainly determined the choice of technique, instead of individual patient characteristics.

Pain response

In total, 241 (74%) of the 325 evaluable patients had a pain response to radiotherapy, with no significant difference between the two treatment techniques (74% each). The pain response rate is comparable to that of the entire DBMS population.

Side effects

Side effects were minor. In general, patients experienced more abdominal complaints than skin complaints. Four and eight weeks after treatment, respectively 264 (77%) and 229 (67%) patients returned questionnaires. Figure 1 shows the course of complaints in the first weeks after treatment. Patients treated with an APPA-technique experienced more abdominal complaints compared to patients treated with a PA-field. This difference was temporary, abdominal complaints were comparable five weeks after treatment. Skin complaints increased minimally over time, irrespective of treatment technique (figure 1A). For both techniques, patients receiving multiple fractions experienced more abdominal complaints than patients receiving a single fraction (figure 1B). Differences in skin complaints were hardly noticed (figure 1C).
In patients treated with both techniques, the course of complaints was similar for all anatomical localizations, although most outspoken for the lumbar spine in patients treated with an APPA technique (figure 2). For skin complaints, only the two patients treated at the lumbo-sacral spine with an APPA-technique showed a distinctive increase, to a maximum mean score of 3.4 (scale of 0-10).
Studying the separate side effects for all 343 patients, a trend was noticed towards more vomiting and abdominal pain in patients treated with the APPA-technique ($p = 0.054$ and $p = 0.053$ respectively). Patients treated with the APPA-technique had significantly more severe complaints of diarrhea ($p = 0.044$). No significant difference was noticed for nausea. Studying the abdominal side effects for the lower spine (all patients, excluding those treated on the thoracic spine only), there were statistically significant differences between treatment techniques. For all studied items (nausea, vomiting, abdominal pain and diarrhea), patients treated with the APPA-technique experienced more complaints than patients treated with the PA-technique (p-values all <0.009).

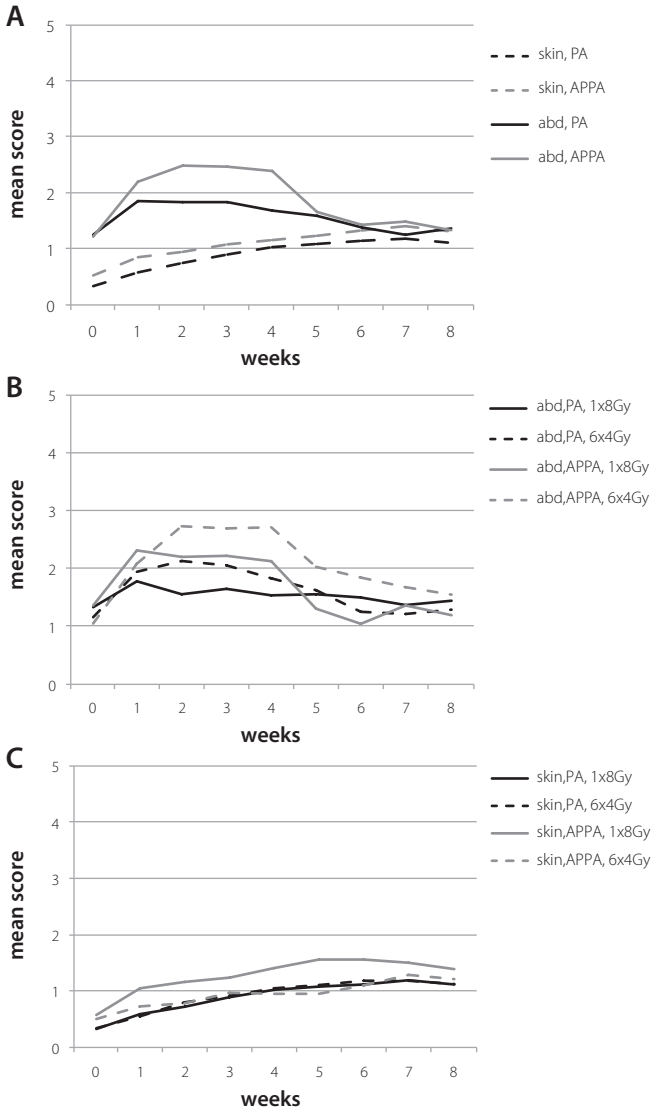

Figure 1 The course of complaints (range of score 0 to 10) after radiotherapy for painful spinal metastases. (**A**) abdominal and skin complaints per treatment technique, (**B**) abdominal complaints per treatment technique and fractionation schedule, (**C**) skin complaints per treatment technique and fractionation schedule.

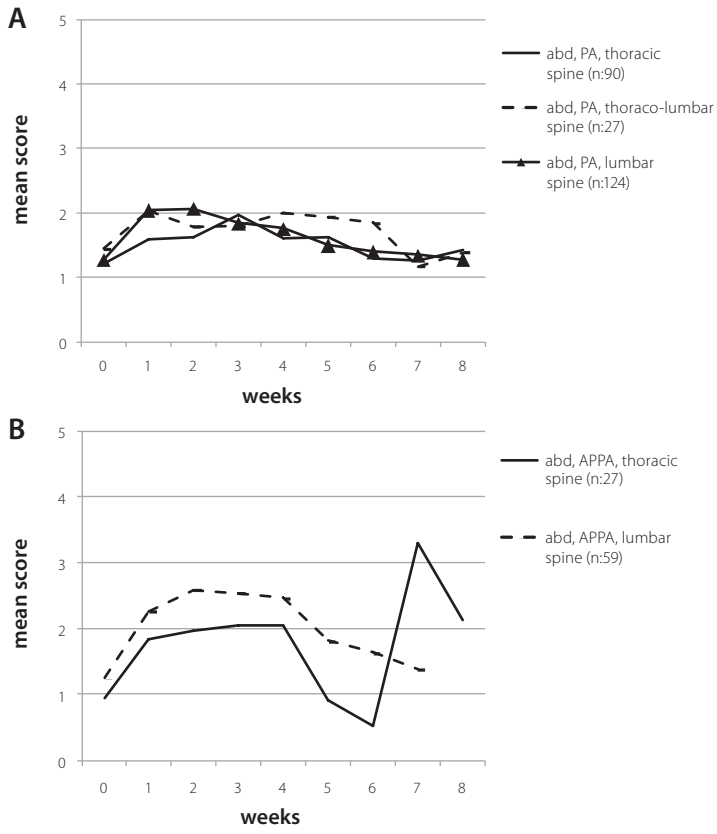

Figure 2 The course of abdominal complaints (range of score 0 to 10) after radiotherapy for painful spinal metastases. To facilitate interpretation, subgroups with less than 10 patients were not shown in the figure (lumbosacral spine PA (n:9), thoracolumbar spine APPA (n:5), lumbosacral spine APPA (n:2)). (**A**) abdominal complaints using the PA-technique per location, (**B**) abdominal complaints using the APPA-technique per location.

Table 2 shows the results of the multivariate analyses. Treatment schedule and location were independent predictors for abdominal complaints. Patients treated with a single fraction had a lower risk of abdominal complaints (OR 0.49 (95% CI 0,29-0,81)) compared to multiple fractions. Patients treated at the thoraco-lumbar and lumbar spine had a higher risk of abdominal complaints (OR 2.51 (0.93-6.80) and 2.29 (1.34-3.93) respectively), compared to radiotherapy of the thoracic spine. For skin complaints (Table 2B), primary tumor and localization were predictive in multivariate analyses. Patients with lung cancer (OR 2.27 (1.20-4.30) compared to breast cancer) had a higher risk of skin complaints.

Patients treated at the lumbo-sacral spine (OR 1.83 (0.52-6.49) compared to radiotherapy of the thoracic spine) had a higher risk, while patients treated at the lumbar spine had a lower risk of skin complaints (OR 0.54 (0.32-0.91)) compared to the thoracic spine.
Treatment technique did not predict for abdominal or skin toxicity after radiotherapy. When studying patients per treatment arm, treatment technique was not significantly associated with abdominal or skin toxicity.

Table 2A Analysis of potential predictors for developing abdominal complaints within four weeks after treatment for painful spinal metastases.

	% of patients with	*Odds Ratio (95% CI)*	
baseline variables	***abdominal complaints***	***UVA [a]***	***MVA [a]***
primary tumor			
breast cancer	73%	1.00	#
prostate cancer	71%	0.90 (0.49-1.67)	
lung cancer	69%	0.84 (0.43-1.64)	
Other	64%	0.68 (0.33-1.42)	
Age			
≤ 65 years	70%	1.00	#
> 65 years	70%	1.01 (0.62-1.64)	
gender			
male	71%	1.00	#
female	70%	0.95 (0.59-1.54)	
KPS			
90 - 100	65%	1.00	#
70 - 80	73%	1.16 (0.61-2.20)	
20 - 60	70%	0.78 (0.39-1.55)	
pain score			
2 - 4	69%	1.00	#
5 - 7	73%	1.22 (0.65-2.30)	
8 - 10	68%	0.96 (0.49-1.86)	
visceral metastases			
no	69%	1.00	#
yes	74%	1.26 (0.72-2.22)	
systemic therapy			
no	73%	1.00	#
yes	68%	0.78 (0.48-1.27)	
treatment schedule			
6 x 4 Gy	78%	1.00	1.00
1 x 8 Gy	63%	0.49 (0.30-0.81)	0.49 (0.29-0.81)

Table 2A Continued.

	% of patients with	*Odds Ratio (95% CI)*	
baseline variables	***abdominal complaints***	***UVA [a]***	***MVA [a]***
pain medication			
no opioids	71%	1.00	#
opioids	70%	0.95 (0.59-1.54)	
spinal localisation			
thoracic spine	60%	1.00	1.00
thoraco-lumbar spine	79%	2.44 (0.91-6.54)	2.51 (0.93-6.80)
lumbar spine	77%	2.22 (1.31-3.77)	2.29 (1.34-3.93)
lumbo-sacral spine	45%	0.56 (0.16-1.94)	0.65 (0.18-2.30)
treatment technique			
PA	69%	1.00	#
APPA	75%	1.35 (0.76-2.37)	

95% CI: 95% confidence interval, UVA: univariate analysis, MVA: multivariate analysis, KPS: Karnofsky performance status, PA: posterior-anterior field, AP-PA: anterior-posterior and posterior-anterior field a: logistic regression analysis, *: the difference is statistically significant, using Chi Square, # : did not remain in the final model

Table 2B Analysis of potential predictors for developing skin complaints within four weeks after treatment for painful spinal metastases.

	% of patients with	*Odds Ratio (95% CI)*	
baseline variables	***skin complaints***	***UVA [a]***	***MVA [a]***
primary tumor			
breast cancer	31%	1.00	1.00
prostate cancer	28%	0.87 (0.47-1.61)	0.95 (0.50-1.79)
lung cancer	49%	2.19 (1.17-4.11)	2.27 (1.20-4.30)
Other	36%	1.26 (0.61-2.62)	1.28 (0.61-2.70)
Age			
≤ 65 years	39%	1.00	#
> 65 years	30%	0.66 (0.41-1.06)	
Gender			
Male	35%	1.00	#
Female	33%	0.92 (0.58-1.47)	
KPS			
90 – 100	34%	1.00	#
70 – 80	31%	0.84 (0.46-1.56)	
20 – 60	40%	1.29 (0.66-2.51)	

Table 2B Continued.

	% of patients with	*Odds Ratio (95% CI)*	
baseline variables	***skin complaints***	***UVA*** [a]	***MVA*** [a]
pain score			
2 – 4	29%	1.00	#
5 – 7	34%	1.22 (0.65-2.31)	
8 – 10	38%	1.48 (0.76-2.90)	
visceral metastases			
No	33%	1.00	#
Yes	38%	1.27 (0.76-2.14)	
systemic therapy			
No	38%	1.00	#
Yes	31%	0.75 (0.47-1.20)	
treatment schedule			
6 x 4 Gy	31%	1.00	#
1 x 8 Gy	37%	1.34 (0.84-2.15)	
pain medication			
no opioids	33%	1.00	#
Opioids	35%	1.09 (0.68-1.75)	
spinal localisation			
thoracic spine	42%	1.00	1.00
thoraco-lumbar spine	39%	0.91 (0.39-2.14)	0.95 (0.40-2.25)
lumbar spine	27%	0.52 (0.31-0.88)	0.54 (0.32-0.91)
lumbo-sacral spine	*55%*	1.69 (0.49-5.89)	1.83 (0.52-6.49)
treatment technique			
PA	*33%*	1.00	#
APPA	*37%*	1.19 (0.70-2.02)	

95% CI: 95% confidence interval, UVA: univariate analysis, MVA: multivariable analysis, KPS: Karnofsky performance status, PA: posterior-anterior field, AP-PA: anterior-posterior and posterior-anterior field a: logistic regression analysis, none of the differences is statistically significant, using Chi Square,
: did not remain in the final model

Discussion

This study showed that treatment technique did not predict for abdominal nor skin complaints. Pain response rates did not differ between both treatment techniques. In a multivariate model, fractionation schedule and treated localization were independent predictors of abdominal complaints. Primary tumor and treated location appeared to be predictors of skin complaints.

Although nowadays more conformal techniques and even stereotactic radiotherapy are frequently used in patients with painful bone metastases, the benefits of those techniques compared to the conventional techniques still remain to be proven. All available data show that a dose higher than 8 Gy is not superior to a single dose of 8 Gy in terms of pain control. [20] These techniques have the disadvantage that they are more time consuming in terms of preparation, additional imaging modalities (such as magnetic resonance imaging) needed and a more complex and technically demanding treatment planning. [21-23] Furthermore, they are more expensive than conventional treatment techniques [24] and treatment time is in general prolonged, which causes more inconvenience for the patients. Therefore, for the majority of patients, conventional techniques still remain the treatment of first choice. [25]

In general, the reported side-effect scores were relatively low. This does not imply that those side effects are not relevant, since even mild complaints might be burdensome. In a study among 368 patients receiving radiotherapy, patients with nausea, although with mild severity in 72% of patients, had a lower QoL and a lower overall level of wellbeing than patients without nausea. [26]

Our results showing more abdominal complaints with the multiple fraction treatment are in line with the results from Chow et al. in re-irradiated patients with painful bone metastases. [27] They described more vomiting, loss of appetite and diarrhea after 20 Gy in multiple fractions compared to a single fraction of 8 Gy. They also described more redness of the skin after multiple fractions, which was not noticed in our analyses, although redness was not specifically questioned.

The abdominal side effects of the APPA-technique were more prominent in patients treated on the lower spine. In this part of the spine, the vertebrae are located relatively ventral. An APPA-technique gives a better dose coverage, due to the deep location of the target volume, with the anterior body of the fifth lumbar vertebra located at a mean depth of 12 cm. [11] A PA-technique might lead to a lower dose on the ventral part of the vertebral body, which can a disadvantage, since previous studies have shown that a dose of 8 Gy results in a higher pain response rate than lower doses. [28, 29] On the other hand, in this study population, the response rate does not differ between treatment techniques.

Another disadvantage of the PA-technique at the lower spine might be the high skin dose when trying to cover the ventral part of the vertebral body. [11] We did not notice skin side effects related to treatment technique, but this might be due to the type of questions asked and the lack of an objective physical examination. An option could be to treat this location with a three field or intensity modulated technique, thereby avoiding bowel structures [30] and the skin. [31, 32] However, these conformal techniques are more time consuming, for patients and logistics [33], and not available in every institution. A more conformal, but efficient and easy technique is a single PA-field using 10MV, with the addition of a second AP-field, contributing less than 50% of the dose, to increase the dose

ventrally to at least 85% of the prescribed dose. In this way, side effects to the bowel can be minimized.

In our multivariate analyses, we found that patients with bone metastases from lung cancer are at increased risk of skin complaints. We have no reason to believe that those patients are more sensitive to radiotherapy. We also found that patients treated at the lumbo-sacral spine have more skin complaints. An explanation might be the varying depth of lumbal and sacral vertebra [11] , possibly leading to more skin dose when trying to cover the entire vertebral bodies with a PA-field. However, we believe those skin complaints to be of minor relevance, due to the limited increase in complaints.

A disadvantage of our analyses is, firstly, that we are not informed about the intake of anti-emetics and/or anti-diarrhea medication. It has been shown that the decision on prescribing medication differs per physician [34], so patients from some physicians might have had medication for side-effects, while others hadn't.. Secondly, the choice of treatment technique was not randomized, increasing the risk of confounding by indication. We did notice a preference per treatment institute. Since institute policy and preferences mainly determined the choice of technique, instead of individual patient characteristics, we also adjusted our analyses for treatment institute as sensitivity analyses, which showed similar outcomes. Thirdly, patients reported their complaints once a week. Perhaps if reported with smaller intervals, minor, but relevant differences in toxicity would have been noted. Fourthly, only 93 patients were treated with the APPA-technique, with a subgroup of 51 patients treated with six fractions of 4 Gy and 42 patients with a single fraction of 8 Gy. Finally, no data were known about dose distribution.

On the other hand, this dataset provides a unique insight in patients receiving palliative radiotherapy, due to the number of patients included and the frequency and contents of the prospective patient-reported follow-up. Although our data were collected from 1996 until 1998, we believe the results presented here are still representative for current patients receiving palliative radiotherapy for spinal metastases, which is still delivered mainly using AP and APPA fields. And, while improvements in systemic therapy have occurred over the last years, the most frequent applied treatment for painful bone metastases is palliative radiotherapy, with a single fraction of 8 Gy as the golden standard [2]. Although medication might help to prevent the reported side effects [35], we believe it is better to try to avoid any side effects by using an optimal treatment technique, especially in this patient group with frequent co-medication and/or systemic therapies.

In conclusion, we advocate the use of a single fraction to treat patients with painful uncomplicated spinal metastases. Based on our analysis, when conventional techniques are used, there is no preference for either a PA or an APPA-technique. If higher total doses are needed, we advise to search for a more conformal treatment technique to avoid high doses to the abdomen, specifically when treating the lower spine.

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4

Screening for psychological distress before radiotherapy for painful bone metastases may be useful to identify patients with high levels of distress

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Abstract

Background: Psychological distress (PD) has a major impact on quality of life. We studied the incidence of PD before and after radiotherapy for painful bone metastases. Furthermore, we aimed to identify factors predictive for PD.

Methods: Between 1996 and 1998, the Dutch Bone Metastasis Study included 1,157 patients with painful bone metastases. Patients were randomized between two fractionation schedules. The study showed a pain response of 74% in both groups. Patients filled out weekly questionnaires for 13 weeks, then monthly for two years. The questionnaires included a subscale for PD on the Rotterdam Symptom Checklist. We used generalized estimating equations and multivariable logistic regression analyses.

Results: At baseline, 290 patients (27%) had a high level of PD. For the entire group, the level of PD remained constant over time. The majority of patients with a low level of PD at baseline remained at a low level during follow-up. In patients with a high level of PD at baseline, the mean level of PD decreased after treatment and stabilized around the cut-off level. Female patients, higher age, worse performance, lower pain score and worse self-reported QoL were associated with an increased chance of PD, although the model showed moderate discriminative power.

Conclusion: A substantial proportion of patients had a high level of PD before and after radiotherapy for painful bone metastases. Most patients who reported high levels of PD when referred for palliative radiotherapy remained at high levels thereafter. Therefore, screening of PD prior to treatment seems appropriate, in order to select patients requiring intervention.

Introduction

Radiotherapy is an effective treatment for patients with painful bone metastases. The pain response rate is above 60%, with the golden standard of a single fraction of 8 Gray (Gy). [1-3] Although reduction of pain is the main treatment goal, it is also important to focus on quality of life (QoL). [4] Painful bone metastases have a negative impact on the QoL of patients. [5, 6] Studies show that radiotherapy stabilizes or improves QoL. [7-15]

Psychological distress (PD) has a major impact on QoL and is defined as a multi-determined unpleasant emotional experience that may interfere with the ability to cope effectively with cancer, its physical symptoms and treatment. [16] Symptoms such as nervousness, depressed mood, worrying, anxiety and irritability contribute to PD [17] and are quite common in patients with advanced cancer. Nervousness for example, is experienced by almost 50% of incurable cancer patients, according to a systematic review in 25.074 patients. [18] Other symptoms, such as depressed mood, worrying, anxiety and irritability are reported by 39%, 36%, 30% and 30% of patients respectively.

Up to 50% of patients suffer from PD, however only a small percentage of them is referred for intervention. [19, 20] Routine screening of distress in patients with disseminated cancer is uncommon [20], despite the fact that several interventions exist which can decrease PD, such as psychosocial interventions [21], cognitive therapy [22] or psycho-educational interventions [23, 24]. Some patients disclose the presence of PD to their health care providers spontaneously and are therefore easily identified. Other patients do not communicate or even recognize their PD and its impact. Patients and health care providers may also be unaware of the possibility of interventions to reduce PD. [19] It is therefore important to identify patients with high levels of PD early, to increase awareness of both patients and health care professionals on this topic, and, if wanted, to offer interventions. Most of the current literature on PD was acquired in patients with cancer treated with a curative intent. [19, 24-28] To our knowledge, no studies were performed so far specifically in patients with bone metastases. No studies reported the extensive course of PD, both in palliative and curative setting.

In earlier publications we showed that total QoL and its separate domains, including the psychosocial domain, diminish towards death [14] and that patients responding to radiotherapy have a better QoL than non-responding patients [29]. The aim of the present analysis was to focus on the incidence of PD in patients with painful bone metastases and its course following palliative radiotherapy. We aimed to identify factors predictive for PD. For this purpose, the data from the randomized Dutch Bone Metastasis Study (DBMS) [1] were used.

Patients and Methods

The DBMS was a nationwide, randomized trial in patients with uncomplicated painful bone metastases. Between 1996 and 1998, 1.157 patients were randomized between a single fraction of 8 Gy or 24 Gy in six fractions. The mean age was 65 years (range, 32-89 years). Fifty-four percent of the patients were male. Most patients had breast cancer (39%), prostate cancer (23%), or lung cancer (25%). At study inclusion, the mean and median time since diagnosis of the primary tumor was more than three years and almost two years, respectively. The median and mean survivals of the entire group were 30 weeks and 49 weeks, respectively, with a range of 0.3 to 142 weeks. The study showed the equal effectiveness of both treatment schedules with regard to pain response, which was the primary endpoint. All patients provided informed consent and the Medical Ethics Committees of participating institutions approved the study. Further details of the DBMS and the study protocol were published elsewhere. [1, 30]

Questionnaires

At randomization and during follow-up, patients filled out weekly questionnaires for thirteen weeks and then monthly until two years of follow-up, death or closure of the study in December 1998. The questionnaires were carried out by mail. The questionnaires consisted, amongst others, of the Rotterdam Symptom Checklist (RSCL) [17], a visual analogue general health scale (VAS-gh), a pain scale and pain medication intake. The RSCL consists of three subscales (psychological distress, physical symptom distress and activity level impairment) and a scale for overall valuation of life (on a seven-point Likert-type scale, with a low score indicating few or no complaints) (VRS-vl). All other RSCL-items were rated on a four-point Likert-type scale, ranging from 1 (no complaints at all) to 4 (many complaints). Sum scores were calculated conform to the manual of the RSCL, inserting the personal scale mean of the patient in cases where less than half of the items of the sum score were missing. [17] At baseline, the score for the RSCL-subscale for PD was available in 94% of patients. In addition to the RSCL scales, a VAS-gh was noted on a line from 0 (no complaints) to 100 (worst general health possible). The advantage of the latter is that each individual patient valuates for himself the impact of his combined physical, psychological and functional condition on their overall perceived general health. Pain was measured using an 11-point numeric rating scale, ranging from 0 (no pain) to 10 (the worst pain imaginable). A pain score of at least 2 was required to enter the study. [1]

Psychological distress

The PD subscale of the RSCL consists of seven items, namely irritability, worrying, depressed mood, nervousness, despairing about the future, tension and anxiety. Since all items are scored on a four-point Likert-type scale, the total sum score ranges from 7 (no PD) to 28 (maximum amount of PD). [17] Ibboston et al. studied the RSCL in 513 cancer

patients, in order to screen for anxiety and depression. The RSCL performed well in patients with progressive disease. A cut-off point with good sensitivity and specificity for the presence of PD was determined at 16. [31]
To determine whether patients with an intermediate level of PD at baseline might have more chance of converting to a high level of PD during follow-up, the patients below the cut-off value were divided into two groups: low (7-11) and an intermediate (12-16) level.

Pain response

Pain response was calculated by taking changes in pain score and pain medication into account, according to international criteria. [32] No fixed time interval from the date of randomization was applied. A response was calculated if at least two successive follow-up pain scores were available.

Statistical analyses

Chi-Square tests were used to compare the categorical variables at baseline. To visualize and compare the course of PD over time, we used generalized estimating equations (GEE-measurements), a longitudinal data analysis technique. P-values are based on two-sided tests and considered significant if $p<0.05$. Figures were created based on the least square means of the repeated measurements.
To assess which variables were predictive for PD at baseline, we dichotomized the patients into having or not having PD (sum score <17 and ≥17). We applied multivariable logistic regression analyses to relate candidate predictors for PD. First, a full model was used, including all preselected variables. Subsequently, we eliminated the variables by a backward selection process with a threshold p-value of 0.20, based on likelihood-ratio test results. The chosen p-value of 0.20 intends to limit the loss of information and to also select weaker predictors, although at the cost of including 'noise' variables. [33] The preselected baseline variables, based on the literature and clinical experience, were primary tumor (breast, prostate, lung or other cancer), age (≤65 or >65 years), gender (male or female), Karnofsky performance status (KPS) [34] (≤ 60, 70-80 or 90-100), baseline pain score (2-5, 6-7 or 8-10), VRS-vl (1-3 (good), 4 or 5-7 (bad)), VAS-gh (0-33 (good), 34-66 or 67-100 (bad)), visceral metastases (yes or no), systemic therapy (yes or no), treatment arm (6x4 Gy or 1x8Gy), pain medication (no opioids or opioids), localization of pain (extremities, spinal column, pelvis or other) and time since diagnosis of primary tumor (continuous). To prevent that independent variables entered into the model were correlated with each other, especially those measuring daily living abilities and general health, we checked for multicollinearity.
The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc, Cary, NC, USA).

Results

Relation between patient characteristics and PD at baseline

In 1084 (94%) patients, the level of PD at baseline could be calculated. The mean level of PD at baseline was 13.4 for the entire group, with a median of 12.0. Twenty-seven percent of patients had a high level of PD at baseline (score≥17). Table 1 shows baseline characteristics of the three baseline levels of PD.

The mean age was 65 years (range 32 – 89 years). Within the different groups of primary cancer, 32% of patients with breast cancer had a high level of distress, compared to 21% of patients with prostate cancer and 22% of lung cancer patients. Twenty percent of male patients experienced a high level of distress, compared to 31% of female patients. There was a significant gender difference in the 285 patients with lung cancer and the fourth group consisting of 145 patients with other primary tumors and their level of PD at baseline. Thirty-seven percent of these women had a high level of PD, compared to 21% of male patients ($p = 0.016$).

There were significant differences between the three groups in terms of primary tumor, gender, KPS, VRS-vl and VAS-gh. Patients with a high level of PD at baseline were more likely to have breast cancer, to be female and to have a low KPS. They had lower scores for their overall QoL, rated both visually and verbally. There was no relation between PD at baseline and mean pain score.

Because we expected patients with a short survival to have high levels of PD, we analyzed this group separately; of the 405 patients who died within three months or did not respond anymore after twelve weeks, 24%, 32% and 44% had a high, intermediate or low level of PD at baseline, respectively. There was no significant correlation between PD at baseline and survival.

Prediction of high levels of PD at baseline

In table 2, the results of multivariate analysis are shown. The final model to predict a high level of PD at baseline included age, gender, KPS, pain score, VRS-vl and VAS-gh. Female patients, higher age, lower performance status, lower pain score and worse self-reported QoL were associated with an increased chance of high levels of PD. The area under the curve of the final model was 0.710, indicating moderate discriminative power. The explained variance was 15.3%.

Course of PD

Figure 1 shows the course of PD over time after treatment. Figure 1a shows the entire group of patients, in which the mean score of distress remained more or less constant over time. When excluding the 405 patients who did not return the questionnaires after three months, due to death (65%) or other reasons, possibly representing patients in a worse clinical condition, the course of PD remains similar, although with slightly lower

Table 1 Baseline characteristics and level of psychological distress.

Baseline variables	*all patients*	*PD low (7 - 11)*	*PD intermediate (12 - 16)*	*PD high (17 - 28)*	*PD unknown*	*p-value*	*differences between (p-value)*
n	1157	457	337	290	73		
Primary tumor						0,016	
Breast	451 (39%)	161 (36%)	129 (38%)	138 (48%)	23 (32%)		low - int: 0.414
Prostate	267 (23%)	111 (24%)	87 (26%)	54 (19%)	15 (21%)		low - high: 0.008
Lung	287 (25%)	119 (26%)	85 (25%)	59 (20%)	24 (33%)		int - high: 0.025
Other	152 (13%)	66 (14%)	36 (11%)	39 (13%)	11 (15%)		
Age						0,308	
≤ 65 years	565 (49%)	218 (48%)	178 (53%)	139 (48%)	30 (41%)		
> 65 years	592 (51%)	239 (52%)	159 (47%)	151 (52%)	43 (59%)		
Gender						<0.001	low - int: 0.471
Male	624 (54%)	268 (59%)	189 (56%)	123 (42%)	44 (60%)		low - high : <0.001
Female	533 (46%)	189 (41%)	148 (44%)	167 (58%)	29 (40%)		int - high: 0.001
KPS						<0.001	
90 – 100	221 (19%)	97 (21%)	80 (24%)	34 (12%)	10 (14%)		low - int: 0.612
70 – 80	592 (51%)	244 (53%)	169 (50%)	145 (50%)	34 (47%)		low - high: <0.001
20 – 60	344 (30%)	116 (25%)	88 (26%)	111 (38%)	29 (40%)		int - high: <0.001
Pain score						0,497	
2 – 5	428 (37%)	172 (38%)	123 (37%)	110 (38%)	23 (32%)		
6 – 7	362 (31%)	144 (32%)	118 (35%)	83 (29%)	17 (23%)		
8 – 10	367 (32%)	141 (31%)	96 (29%)	97 (33%)	33 (45%)		
VRS-vl						<0.001	low - int: <0.001
1-3	350 (30%)	189 (41%)	92 (27%)	48 (17%)	21 (29%)		low - high : <0.001
4	364 (32%)	152 (33%)	113 (34%)	75 (26%)	24 (33%)		int - high: <0.001
5-7	443 (38%)	116 (25%)	132 (39%)	167 (58%)	28 (38%)		

Table 1 Continued.

Baseline variables	*all patients*	*PD low (7 - 11)*	*PD intermediate (12 - 16)*	*PD high (17 - 28)*	*PD unknown*	*p-value*	*differences between (p-value)*
n	1157	457	337	290	73		
VAS-gh						<0.001	
0-33	236 (20%)	127 (28%)	71 (21%)	30 (10%)	8 (11%)		low - int: 0.043
34-66	530 (46%)	220 (48%)	164 (49%)	108 (37%)	38 (52%)		low - high: <0.001
67-100	391 (34%)	110 (24%)	102 (30%)	152 (52%)	27 (37%)		int - high: <0.001
Visceral metastases						0,904	
No	838 (72%)	331 (72%)	244 (72%)	214 (74%)	49 (67%)		
Yes	319 (28%)	126 (28%)	93 (28%)	76 (26%)	24 (33%)		
Systemic therapy						0,205	
No	531 (46%)	215 (46%)	156 (46%)	118 (41%)	42 (57%)		
Yes	626 (54%)	242 (54%)	181 (54%)	172 (59%)	31 (43%)		
Treatment arm						0,215	
6x4 Gy	578 (50%)	218 (48%)	180 (53%)	138 (48%)	42 (58%)		
1x8 Gy	579 (50%)	239 (52%)	157 (47%)	152 (52%)	31 (43%)		
Pain medication						0,112	
No opioids	667 (58%)	279 (61%)	200 (59%)	155 (53%)	33 (45%)		
Opioids	490 (42%)	178 (39%)	137 (41%)	135 (47%)	40 (55%)		
Localization of pain						0,41	
Extremities	173 (15%)	76 (17%)	45 (13%)	44 (15%)	8 (11%)		
Spinal column	345 (30%)	119 (26%)	109 (32%)	93 (32%)	24 (33%)		
Pelvis	455 (39%)	183 (40%)	134 (40%)	109 (38%)	29 (40%)		
Other	184 (16%)	79 (17%)	49 (15%)	44 (15%)	12 (16%)		

* : Pearson Chi-Square, KPS: Karnofsky performance score, VRS-vl: verbal rating score, valuation of life
VAS-gh: visual analogue score of general health, VRS-vl and VAS-gh: the lower, the better QoL, Gy: Gray

Table 2 Univariate (UVA) and final multivariate (MVA) logistic regression analyses on potential baseline predictors for high level of psychological distress before palliative radiotherapy for painful bone metastases.

Baseline variables	*Odds ratio (95% CI)*	
	UVA*	**MVA***
Primary tumor		
Breast	1.00	#
Prostate	0.57 (0.40 - 0.82)	
Lung	0.61 (0.43 - 0.87)	
Other	0.80 (0.53 - 1.22)	
Age		
≤ 65 years	1.00	1.00
> 65 years	1.08 (0.83 - 1.42)	1.28 (0.95 - 1.73)
Gender		
Male	1.00	1.00
Female	1.84 (1.40 - 2.42)	1.94 (1.44 - 2.62)
KPS		
90-100	1.00	1.00
70-80	1.83 (1.21 - 2.76)	1.44 (0.92 - 2.24)
20-60	2.83 (1.84 - 4.37)	1.67 (1.03 - 2.70)
Pain score		
2 – 5	1.00	1.00
6 – 7	0.85 (0.61 - 1.18)	0.65 (0.46 - 0.94)
8 – 10	1.10 (0.80 - 1.52)	0.60 (0.42 - 0.87)
VRS-vl		
1 – 3	1.00	1.00
4	1.66 (1.11 - 2.47)	1.40 (0.91 - 2.17)
5 – 7	3.94 (2.74 - 5.67)	2.54 (1.63 - 3.96)
VAS-gh		
0-33	1.00	1.00
34-66	1.86 (1.20 - 2.88)	1.43 (0.88 - 2.31)
67-100	4.73 (3.06 - 7.32)	2.64 (1.55 - 4.48)
Visceral metastases		
No	1.00	#
Yes	0.93 (0.69 - 1.26)	
Systemic therapy		
No	1.00	#
Yes	1.28 (0.97 - 1.68)	
Treatment arm		
6 x 4 Gy	1.00	#
1 x 8 Gy	1.11 (0.85 - 1.45)	

Table 2 Continued.

Baseline variables	*Odds ratio (95% CI)*	
	UVA*	**MVA***
Pain medication		
No opioids	1.00	#
Opioids	1.32 (1.01 - 1.74)	
Localization of pain		
Extremities	1.00	#
Spinal column	1.12 (0.74 - 1.71)	
Pelvis	0.95 (0.63 - 1.42)	
Other	0.95 (0.58 - 1.54)	
Time since primary tumor		
(Continuous)	1.00 (1.00 - 1.00)	#

95% CI: 95% confidence interval, UVA: univariate analysis, MVA: multivariate analysis, *: logistic regression analysis, #: did not remain into the final model, KPS: Karnofsky performance score, VRS-vl: overall valuation of life, VAS-gh: visual analogue score of general health. VAS-gh, VRS-vl: the lower the score, the better QoL

scores (figure 1a).When separating the patients into three groups with low, intermediate and high PD at baseline, figure 1b shows that the course of distress was also rather stable for the low and intermediate group. For patients with a high level of distress at baseline, the mean level decreased in the first weeks after treatment and stabilized around 16 (slightly below the cut-off level).

Sixty percent of patients with an initially high level of PD never reached a period of several weeks with PD below the threshold value. Of the patients with low or intermediate PD at baseline, approximately 20% were above the cut-off value of 17 somewhere in the follow-up period. No major differences in the course of distress between the four different primary tumors groups were noticed.

Figure 2 shows the proportion of patients with a high, intermediate or low level of PD. The percentage of patients with a high level of PD decreases slightly over time, but remains substantial during the follow-up.

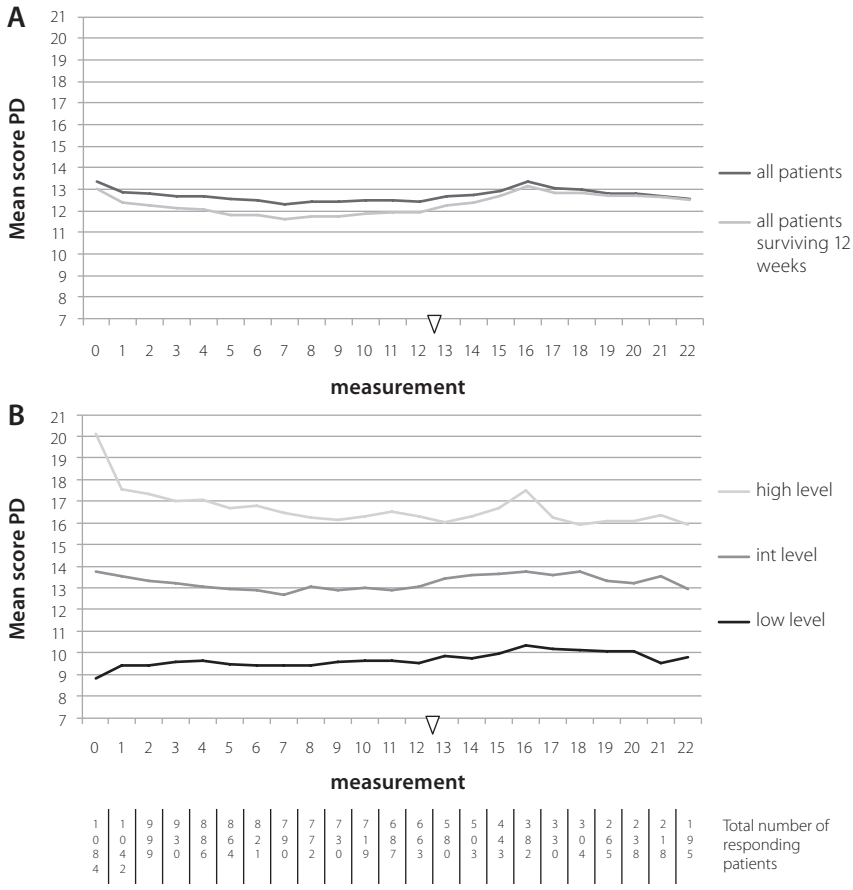

Figure 1 Mean scores of psychological distress (sum score ranges between 7 (low) and 28 (high)) at baseline (measurement 0) and after radiotherapy for painful bone metastases in (**A**) All patients (n = 1084) and all patients who still returned their questionnaires after twelve weeks (n = 679) and (**B**) Patients with a high (n = 290), intermediate (n = 337) and low level (n = 457) of psychological distress at baseline. The first twelve measurements after baseline were taken weekly, thereafter monthly.

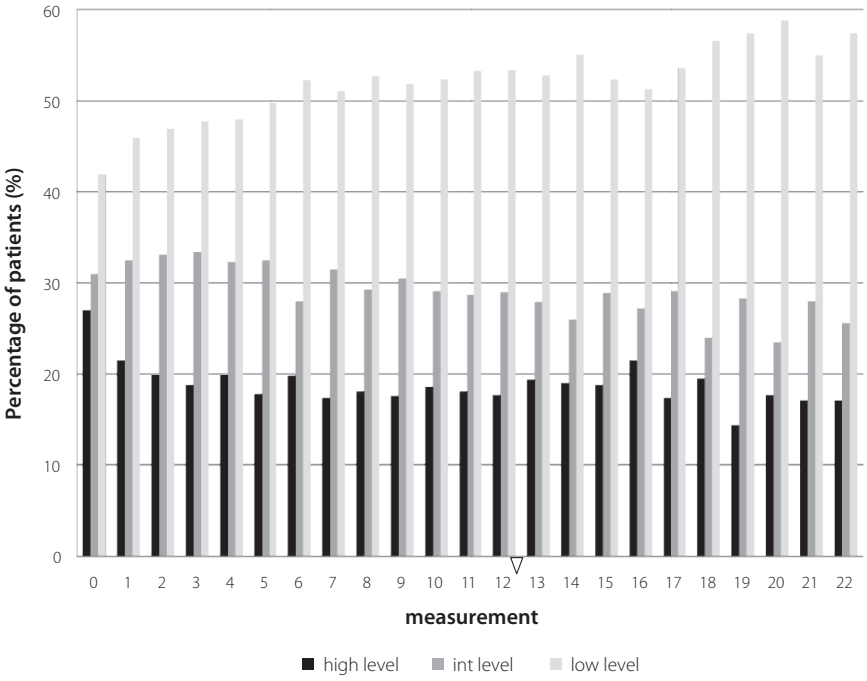

Figure 2 Percentage of patients with a low, intermediate or high level of PD during follow-up. The first twelve measurements after baseline were taken weekly, thereafter monthly.

Discussion

We conclude from our analyses that 27% of patients with advanced cancer referred for palliative radiotherapy for painful bone metastases, have a high level of psychological distress when measured on the Rotterdam Symptom Checklist. [17] Furthermore, we showed that female patients, older patients , those with a bad performance score, lower pain score and a low self-reported QoL are at risk for a high level of PD.

The course of PD following radiotherapy depends mainly on the level of PD at the start of treatment. In patients with high levels of distress at baseline the mean level of PD declined to a level just above the cut-off for having complaints. This might be due to (the expectation of) a pain response or the attention of caregivers at the radiotherapy department, even though, 19% of patients experienced high psychological distress a few weeks after treatment. There is little change in the level of distress after treatment in patients with intermediate and low levels of distress at baseline.

The results may be influenced by the loss of follow-up, as three months after treatment only 663 patients (57%) returned questionnaires. This is of course mainly due to the study population of patients with metastasized cancer and a limited life expectancy. Theoretically this might influence the results, since after a few months only the fittest patients remain, who may be less distressed than those patients approaching death. Therefore, in figure 1a, we excluded patients with a relatively short survival or those who were lost to follow-up three months after treatment. When excluding those patients, the course of PD remains similar, although this population has a slightly lower level of PD.

The World Health Organization has defined palliative care as "an approach that improves the QoL of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual". [35] In patients with advanced cancer, however, both patients and their health care provider are often focused on physical symptoms, with less attention for psychosocial problems. Although PD is a common problem among patients with cancer, many of those patients are not recognized and referred for interventions. [19, 20] Several interventions for coping with PD exist, such as individual psychological support, support groups or education programs. [20, 21, 36] Therefore, screening might be considered. A large recent review concluded that no specific screening tool for distress could be recommended [20]. A screening tool which is often used in Dutch hospitals, the distress thermometer (Lastmeter) [26], uses dichotomized questions such as 'do you feel distressed', supplemented with the amount of distress on a scale from 0 to 10. A review including seven randomized trials showed that screening showed an effect on psychological well-being in four of the seven trials. [37] Furthermore, screening seems to improve communication between health care providers and patients and may enhance psychosocial referrals and facilitate discussions about QoL. [20] However, it is important to be aware that not all patients with a high level of PD want to be referred for an intervention. [26] In a study in 302 cancer patients in the Netherlands, mostly treated with curative intent, 51% of distressed patients did not need an intervention directly after treatment and 25% were already receiving support. After two months, regardless of distress level, 10% of all screened patients reported an unmet need for intervention. The study showed that the need for an intervention was positively related to the level of distress. [28] In a study evaluating 361 referrals for psycho-oncological counseling, 20% of newly referred patients never attended counseling. These patients were mainly men and patients with lung cancer. [36] Therefore, although identification of distress is important in order to identify those patients who might benefit from intervention, referral should be discussed with the individual patient. A study in 1352 Dutch cancer patients found that single patients, patients not living with their partner and patients below 65 years most often wanted an intervention when highly distressed. [27] In Switzerland, a study investigating the barriers

and predictors of patients accepting or declining psycho-oncological support has recently opened. The results of this trial should increase the insight into why not all patients with PD want to be referred for an intervention. [38]

To our knowledge, no other papers regarding the incidence and course of PD in patients with bone metastases treated with palliative radiotherapy have been published, making it difficult to compare our results with other studies. A Japanese study in 85 patients with advanced non-small cell lung cancer, measured PD at diagnosis, after two and six months. Forty percent of these patients underwent radiotherapy. They showed that depression and anxiety decreased over time, while other dimensions of PD and the overall level of PD did not. A high level of complaints at baseline predicted for a high level of complaints during follow-up. Therefore, the authors recommended starting an intervention shortly after diagnosis. [39] These findings are largely in line with our results, although we notice a decrease in overall level of PD in patients with a high level of PD at baseline.

A study among 149 married cancer patients, mainly with advanced disease, showed that female patients reported a higher overall distress than male patients. [40] In the earlier mentioned Dutch study in 302 cancer patients, female patients and younger patients were at higher risk of having a high level of PD. [28] In another paper studying 2.776 patients with cancer visiting a tertiary cancer center in Canada, significant gender differences were found; female patients reported depressive symptoms more frequently than male patients and were more likely to receive psychosocial support. [19] Contrary to our results, they also found younger patients to be at a higher risk of PD [19], as did a recent study among breast cancer patients in Morocco [25]. This might be related to the study populations, namely patients with all stages of cancer, where the disruption of social life might be different compared to patients in the palliative phase.

Surprisingly, the three groups of PD had comparable pain scores at baseline. One would expect a higher pain score to be a risk factor for PD, leading to more anxiety, worrying or depression. Accordingly, in a study among 106 palliative patients a higher pain score was correlated with increased distress. [41] In contrast, we found that a lower pain score predicted for a higher level of PD. We have no clear explanation for this finding.

Our data were collected in the late nineties, which might be considered as a limitation of our study, since changes in treatment and subsequent survival may have altered the course of the disease. Nevertheless, it is based on a unique and large cohort of patients with bone metastases. Although the systemic treatment has changed over time, the standard local treatment for patients with painful bone metastases has remained palliative radiotherapy, with a single fraction of 8 Gy. [2] Therefore, we believe these results are still applicable to current patients with painful bone metastases. Another possible shortcoming could be that we did not study patients with painful bone metastases who did not receive radiotherapy. The course of PD could be a result of progressive disease.

In conclusion, over 25% of patients referred for palliative radiotherapy for painful bone metastases have high levels of PD at baseline, which slightly decreases in the months

following treatment. Although palliative radiotherapy is an effective treatment for pain, these patients still experience distress. Therefore, we would like to increase awareness in referring medical specialists and radiation oncologists on the presence of PD. We advise them to screen patients for PD and, if present, to make the topic discussable. If wished for, interventions should be offered, in order to maintain or further improve QoL of their patients.

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5

Course of quality of life after radiation therapy for painful bone metastases – a detailed analysis from the Dutch Bone Metastasis Study

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Abstract

Purpose: To study the course of quality of life (QoL) after radiation therapy for painful bone metastases

Methods: The Dutch Bone Metastasis Study randomized 1157 patients with painful bone metastases between a single fraction of 8 Gray and six fractions of 4 Gray between 1996 and 1998. The study showed a comparable pain response of 74%. Patients filled out weekly questionnaires for 13 weeks, then monthly for two years. In these analyses, physical, psychosocial and functional QoL domain scores and a score of general health were studied. Mixed modeling was used to model the course of QoL and to study the influence of several characteristics.

Results: In general, QoL stabilized after a month. Psychosocial QoL improved after treatment. The level of QoL remained stable, steeply deteriorating at the end of life. For most QoL domains, a high pain score and intake of opioids were associated with worse QoL, with small effect sizes (-0.11 to -0.27). A poor performance score was associated with worse functional QoL, with a medium effect size (0.41). There is no difference in QoL between patients receiving a single fraction of 8 Gray and six fractions of 4 Gray, except for a temporary worsening of physical QoL after six fractions.

Conclusion: Although radiation therapy for painful bone metastases leads to a meaningful pain response, most domains of QoL do not improve after treatment. Only psychosocial QoL improves slightly after treatment. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterward a sharp decrease, starting only a few weeks before the end of life. Six fractions of 4 Gray lead to a temporary worse physical QoL compared with a single fraction of 8 Gray.

Introduction

Radiation therapy is an effective treatment for patients with painful bone metastases, with a pain response rate of more than 60%. Several randomized trials have shown an equal effectiveness in pain response of a single fraction of 8 Gray (Gy) compared to multiple fractions. Therefore, the golden standard is to treat these patients with a single fraction of 8 Gy. (1-3) Although reduction of pain is the main aim of treatment in patients with painful bone metastases, it is also important to focus on other goals of treatment. In the palliative setting, the traditional oncological treatment endpoints, like disease control or survival are often less or even not appropriate. The treating physician has to weigh the impact of treatment against the benefit it provides for the individual patient. Therefore, palliative treatments focus on maintaining or improving quality of life (QoL). (4)

Health-related QoL is defined as a multidimensional construct encompassing perceptions of both positive and negative aspects of physical, emotional, cognitive and social functions, due to the sequelae of a disease and its treatment. (5) Painful bone metastases have a negative impact on the QoL of patients. (6, 7) Despite this, few of the numerous randomized trials that were published since the late nineties documented the impact of bone metastases and its treatments on QoL. If patients and their treating doctors have a better understanding of the expected course of QoL, this may help them to make decisions about treatment of painful bone metastases in the context of a possibly short life expectancy.

Some studies reported that radiation therapy improved QoL, mainly in patients experiencing a pain response. (8-14) Two of these publications had a very short follow-up of only one month (10, 11) and only two studies were randomized (12, 13). One of the latter studies compared different treatment schedules and found that improvements of QoL were of similar magnitude irrespective of fractionation schedule (single or multiple fractions). (12) The second, more recent, randomized study compared two treatment schedules for re-irradiation of painful bone metastases and found a better QoL two months after retreatment in responders compared to non-responders. (13) None of these studies reported the course of specific domains of QoL after treatment.

Initial analyses of the Dutch Bone Metastasis Study (DBMS), the largest randomized trial comparing the effect of single versus multiple fractions on pain response, found no differences in global QoL between patients treated with a single fraction and multiple fractions. (1, 15) More recent analyses report that patients responding to radiation therapy have a better QoL during the first three months after treatment than non-responding patients. (16) The aim of our current analysis was to study the detailed course of the physical, psychosocial and functional domains of QoL and general health after radiation therapy for painful bone metastases with a maximum of two years follow up after treatment, and to create a model of its course. We also analyzed the influence of baseline and follow-up variables on the course of QoL.

Patients and methods

The DBMS was a nationwide randomized controlled trial in 17 out of the 21 radiation therapy institutions for patients with painful bone metastases in the Netherlands. Between 1996 and 1998, a total of 1157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or 24 Gy in six fractions. The main endpoint of the study was pain response. Detailed descriptions of the study protocol have been published previously. (1) The Medical Ethics Committees of participating institutions approved the study and all patients provided informed consent. The database was updated for survival and closed in December 1998.

Questionnaires

At randomization and during follow-up, patients filled out weekly questionnaires for thirteen weeks and monthly thereafter until two years of follow-up, death or closure of the study. These questionnaires contained in total 43 items, including items from the Rotterdam Symptom Checklist (RSCL) (17), three questions about possible side-effects of radiation therapy and two questions from the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of life Questionnaire (QLQ)-C30 (18), whether physical condition or medical treatment influenced family life or social activities. Furthermore, questionnaires consisted of a visual analogue general health scale (VAS-gh) and a question on the intake of pain medication. At randomization, the treating physician rated the performance using the Karnofsky performance status (KPS) (19). Pain was measured using an 11-point numeric rating scale, ranging from 0 (no pain) to 10 (worst pain imaginable). A pain score of at least 2 was required to enter the study. (1) The VAS-gh is a self-reported global assessment of general health, which was noted on a line from 0 (no complaints) to 100 (worst general health possible). Missing data were imputed using the expectation maximization algorithm, when patients filled out at least half of the questionnaires. Of all questionnaires, 67.5% were filled out completely, without missing values. Twenty-two percent of all questionnaires were missing only one value.

Quality of life analyses

In total, data of 1115 patients (96,4%) were used. The remaining 42 patients were not analyzed, since they never filled out a (complete) questionnaire. Principal component analysis with oblique rotation was used to reduce the number of QoL items from the questionnaires into components (or domains). Principal component analysis is considered a valid method to summarize data into factor scores. The advantage of this method is that we were able to convert individual items from the different questionnaires that were used in the DBMS into clinically meaningful and relevant sum scores. Three domains were found and labeled as: physical health, psychosocial health and functional status. Table 1 presents the rotated and standardized component loadings, with a score for the contributive

ability of the item on the domain. As shown in table 1, some of the items contribute to two or three domains, while others contribute to a single domain. The domain scores were standardized to scores (z-scores), with a mean of 0 and a standard deviation of 1, to facilitate interpretation of the subsequent regression analyses. The domain z-scores were used for further analyses. A multilevel regression analysis was used to study the course of QoL (the three domain scores and the VAS-gh) during follow-up and to create a model based on these patient data. The higher the total score, the better the QoL. The multilevel model enables the analysis of all available data, as opposed to only complete data. The repeated measures have a first-order autoregressive covariance structure. We studied the influence of the following baseline variables on the course of QoL: age, gender, KPS, primary tumor (breast, prostate, lung cancer, and other) and treatment arm (1x8Gy, 6x4Gy). In addition, we studied the influence of two variables varying over time: pain score and intake of opioids. An alpha level of 0.05 was used to judge statistical significance of effects. As both predictors and outcome variables have been standardized, the regression coefficients can be interpreted as effect size r and d for continuous and dichotomous predictors respectively. Regression coefficients for binary predictors can be interpreted as effect size Cohen's d, with values of 0.2-<0.5, 0.5-<0.8, and ≥0.8 indicating small, medium and large effect sizes, and regression coefficients for continuous predictors can be interpreted as effect size r, with values of 0.1-<0.3, 0.3-<0.5, and ≥0.5 indicating small, medium and large effect sizes. (20, 21) Negative values indicate a negative effect on QoL, positive values a positive effect.

Survival groups for the course of QoL

To identify the course of QoL in relation to remaining survival, we divided patients into five separate survival groups, with an observed survival of less than 3, 3-<6, 6-<12, 12-<18 and 18-<24 months. QoL was modeled as a composite of two latent curves, modeling both time since the first measurement and time to death. This model thus takes into account the impact of impending death, as this can have a marked impact on QoL. The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

Table 1 Allocation of the variables to the three QoL domains, with accompanying standardized component loadings.

Source	Items	physical	psychosocial	functional
RSCL	lack of appetite	0.49		0.26
	irritability		0.59	
	tiredness	0.44	0.30	
	worrying		0.91	
	sore muscles	0.38		
	depressed mood		0.87	
	lack of energy	0.34	0.46	
	low back pain	0.41		
	nervousness		0.83	
	nausea	0.62		
	despairing about future		0.90	
	difficulty sleeping	0.29	0.31	
	headaches	0.45		
	vomiting	0.54		
	dizziness	0.52		
	decreased sexual interest		0.25	
	tension		0.85	
	abdominal (stomach) aches	0.55		
	anxiety		0.91	
	constipation	0.40		
	diarrhoea	0.30		
	acid indigestion	0.59		
	shivering	0.49		
	tingling hands or feet	0.43		
	difficulty concentrating	0.26	0.45	
	sore mouth/pain when swallowing	0.49		
	loss of hair	0.20		
	burning/sore eyes	0.44		
	shortness of breath	0.31		
	dry mouth	0.53		0.21
	care for myself (wash etc.)			0.82
	walk about the house			0.83
	light housework/household jobs			0.84
	climb stairs			0.85
	heavy housework/household jobs			0.85
	walk out of doors			0.88
	go shopping			0.86
	overall valuation of life	0.40	0.28	0.29

Table 1 Continued.

Source	Items	physical	psychosocial	functional
QLQ-C30	interference with family life		0.31	0.34
	interference with social activities		0.30	0.47
added questions	itching	0.45		
	painful skin	0.42		
	bone pain	0.37	0.20	

To facilitate interpretation of the domains, we only display items with a factor loading equal to or larger than 0.20, RSCL: Rotterdam Symptom CheckList; QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of life Questionnaire

Results

General outcome

The primary results of the DBMS were already published. (1, 15) In short, of the 1115 evaluable patients, the mean age was 65 years (range 32-89 years) and 46% of patients was female. The mean KPS was 70 (range 20-100) and in 28% of patients visceral metastases were documented. The most common primary tumors were breast (39%), prostate (23%) and lung cancer (25%). The overall pain response rate was 74%, with no difference between the two treatment schedules. The median and mean survivals were 30 and 49 weeks respectively, with a range of 0.3-142 weeks. After one year, 320 patients (28%) were still alive and returning questionnaires. At closure of the study, with a maximum follow-up of 142 weeks (≈ 2.7 years) 860 (74%) patients had died.

Quality of life

Figure 1 shows the modeled course of the QoL domains physical health, psychosocial health and functional status and of the VAS-gh in patients surviving less than 3, 3-<6, 6-<12, 12-<18 and 18-<24 months after randomization, respectively. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterwards a sharp decrease, starting several weeks before the end of life. In general, treatment with radiation therapy does not lead to an improvement of QoL. After start of treatment, immediate deteriorations in the first week of the physical domain, the functional domain and VAS-gh are noticed. For the physical domain only, an improvement is seen after this initial decline. In both other domains, the deterioration flattens until it further decreases near death. Only in the psychosocial domain an improvement after treatment occurs, which persists until the steep decline towards death.

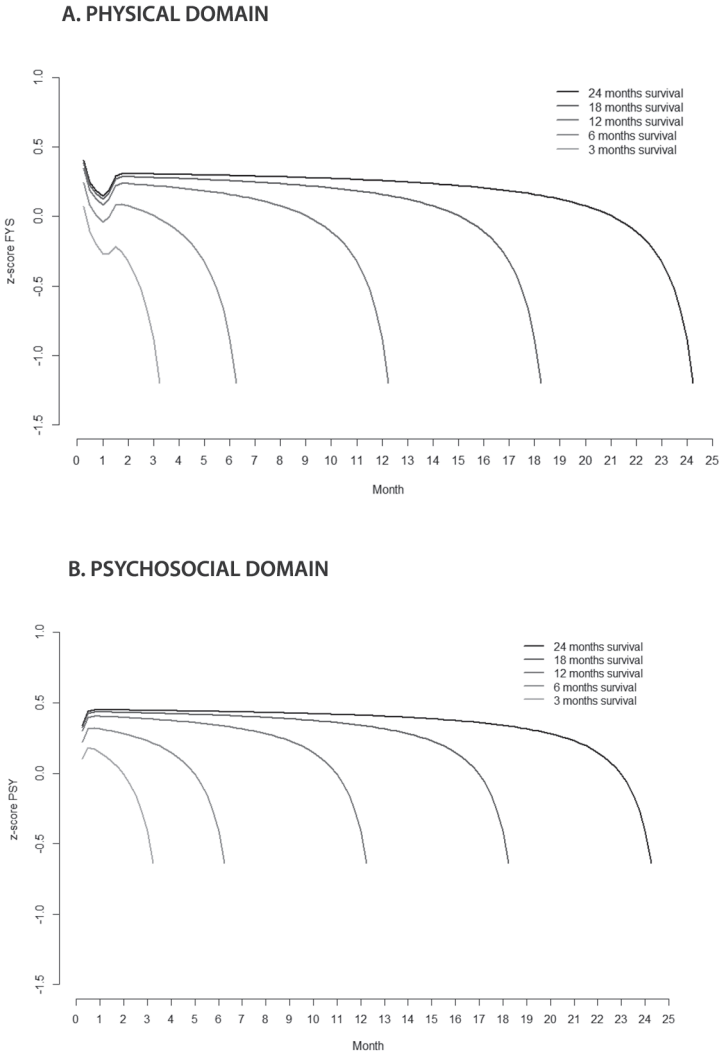
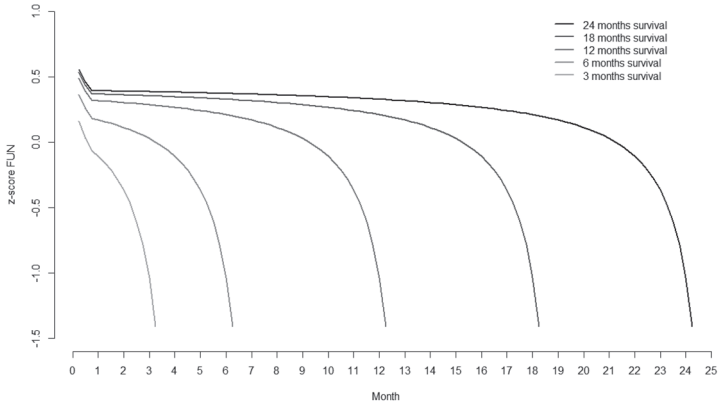


Figure 1 The modeled course of QoL after radiation therapy for painful bone metastases, represented in survival groups (patients surviving less than 3, 3-<6, 6-<12, 12-<18 and 18-<24 months after randomization). The x-axis represents the months after treatment, where month 0 is the baseline measurement before treatment and month 1 the first months after treatment. The y-axis reflects the domain score of QoL, where the average is 0, with a standard deviation of 1. The higher the score, the better the QoL. (**A**) physical domain. (**B**) psychosocial domain. (**C**) functional domain. (**D**) VAS-gh.

C. FUNCTIONAL DOMAIN



D. VAS-gh

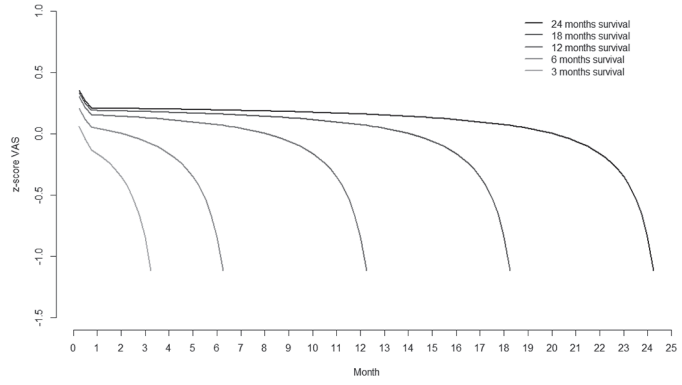


Figure 1 Continued.

Impact of baseline and follow-up variables on QoL

Table 2 describes which baseline and follow-up variables influenced the course of the different QoL domain scores and the VAS-gh, including the effects sizes. Higher pain score and intake of opioids are associated with lower levels of QoL for almost all domains, with varying effect sizes. There are small, but clinically relevant, effects of intake of opioids on the physical and functional domain and on VAS-gh (-0.27, -0.21 and -0.21 respectively) and of pain score on the physical and psychosocial domain and on VAS-gh (-0.14, -0.11 and -0.24 respectively). The largest effect size is for the influence of KPS on the functional domain, with a medium effect size of 0.41. Age has a small effect on the functional domain, of -0.12. Thus, a lower baseline performance score or higher age is associated with significantly worse functional status. Furthermore, primary tumor has a small effect on the physical and functional domain, with patients with prostate cancer having worse functional and physical QoL after radiation therapy, while patients with breast cancer have a worse functional QoL, compared to patients with other types of cancer. Other effect sizes are smaller and therefore not considered clinically relevant.

Impact of treatment schedule on QoL

Patients receiving either 8 Gy in a single fraction or six fractions of 4 Gy have comparable QoL outcomes, except for the physical domain (Figure 2). Treatment with six fractions of 4 Gy leads to a temporary worsening of QoL on the physical domain during the first four weeks after treatment, compared to a single fraction of 8 Gy. This is represented in the difference between the dotted and the solid line in figure 2, with superimposing lines afterwards (effect size each week below 0.2, indicating a minor effect, $p<0.001$, table 2).

Table 2 Influence of baseline and follow-up variables on QoL domains, with effect sizes.

	QoL domains							
	physical		psychosocial		functional		VAS-gh	
Variables	***effect size***	***p-value***	***effect size***	***p-value***	***effect size***	***p-value***	***effect size***	***p-value***
Baseline:								
age	0.01	0.72	0.03	0.24	**-0.12**	<0.001	0.01	0.65
gender	-0.11	0.26	-0.17	0.11	-0.19	0.02	-0.06	0.45
(reference: male)								
KPS	0.00	0.93	0.06	0.04	**0.41**	<0.001	0.09	<0.001
primary tumor *(reference: other)*								
breast	-0.08	0.43	-0.12	0.28	**-0.27**	0.002	-0.14	0.11
prostate	**-0.20**	0.03	-0.18	0.06	**-0.22**	0.003	-0.11	0.11
lung	0.06	0.44	-0.04	0.63	-0.10	0.16	0.00	0.95
Follow-up:								
treatment arm	-0.12 – -0.17 *	<0.001	0.06	0.24	0.02	0.57	0.03	0.42
(reference: 1x8Gy)								
pain score	**-0.14**	<0.001	**-0.11**	<0.001	-0.07	<0.001	**-0.24**	<0.001
intake of opioids	**-0.27**	<0.001	-0.05	0.001	**-0.21**	<0.001	**-0.21**	<0.001
(reference: no opioids)								

KPS : Karnofsky performance status, VAS-gh: visual analogue scoring of general health

Binary variables (gender, primary tumor, treatment arm and intake of opioids): Effect sizes between -0.19 and 0.19 are considered minor effects and are not clinically relevant.

Continuous variables: Effect sizes between -0.09 and 0.09 are considered minor effects and are not clinically relevant. To facilitate interpretation, clinically relevant effects are printed bold. A positive direction of the effect size means improvement of QoL by increase of the variable / compared to the reference

* The effect size varies each week, ranging from -0.12 (week 4), -0.13 (week 2) to -0.17 (week 3)

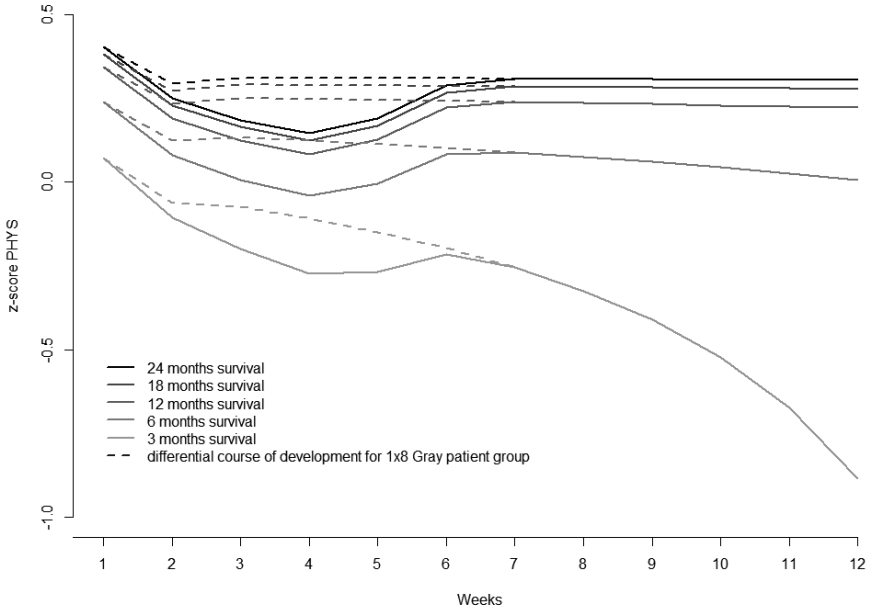


Figure 2 The modeled course of the physical domain twelve weeks after randomization, represented in survival groups (patients surviving less than 3, 3-<6, 6-<12, 12-<18 and 18-<24 months after randomization). The temporary difference between both fractionation schemes is shown in the dotted line (1x8 Gray) and the solid line (6x4 Gray). The x-axis represents the weeks after start of treatment. The y-axis reflects the physical domain score, where the average is 0, with a standard deviation of 1. The higher the score, the better the physical QoL.

Discussion

Our analyses describe the detailed course towards death of different QoL domains after radiation therapy in patients with painful bone metastases. QoL initially remains stable after treatment, until a steep deterioration occurs near the end of life. It is an important finding for both patients and physicians to be aware of the rather stable QoL, until several weeks before death. This stabilization may reflect the benefit of treatment, since a decline can be expected without treatment in most patients. However, since untreated patients were not studied, it may also reflect the natural course of the disease in these patients. The course of QoL towards death is in accordance with the pattern described by Murray. (22) His paper, which is frequently cited in palliative care, shows a distinctive pattern for cancer

patients versus patients with other life threatening diseases, such as COPD and cardiac failure. Cancer patients show a predictable pattern, characterized by an initial rather stable course of QoL, followed by a short and swiftly declining phase towards death. Our model, based on actual patient data, therefore confirms the hypothesis by Murray also for patients with painful bone metastases.

There seems to be a discrepancy in our results that, although 74% of patients experienced a pain response, most domains of QoL of these patients did not improve after radiation therapy. This is in line with the fact that we found little effect in the multilevel regression analyses of pain score on the QoL domains. The main reason for this is probably the influence of many other variables on QoL, like the presence of other symptoms these patients suffer, related to their advanced disease and possibly also side effects from medication and/or systemic therapies. Concerns about end-of-life and worrying about the future might also influence QoL. (23) These concerns are not likely to resolve after radiation therapy for painful bone metastases. Nevertheless, in a population like this, even stabilization of QoL may be considered very meaningful to patients. Without treatment, QoL might have deteriorated sooner. The improvement in psychosocial status after treatment, might be due to the care given by doctors and nurses at the radiation therapy department, in combination with the hope and expectation of a beneficial treatment outcome. Notable is the temporary decline of physical health after six fractions of 4 Gy, which does not occur after a single fraction of 8 Gy, although with a minor effect size. The difference may be due to more treatment side effects and the burden of five additional visits to the radiation therapy facility.

On the one hand, our results, indicating no apparent improvement of QoL after radiation therapy for painful bone metastases, are in line with the results from Caissie et al (8). They prospectively studied the QoL of a cohort of 178 patients with uncomplicated painful bone metastases, using the EORTC-QLQ-C15-PAL questionnaire at one, two, four and eight weeks after treatment. Unfortunately, at three out of the four time points a maximum of 40% of patients returned the questionnaires. The pain response rate was 65% after two months. They reported no improvement of total QoL up to two months after radiation therapy, while pain, insomnia and constipation improved. In a recent randomized study on retreatment for painful bone metastases, in 528 evaluable patients, no clinically relevant improvement of global QoL was noticed after a pain response. (13)

The results of the present study seem to be in contradiction with our earlier analyses showing that responders have a better QoL compared to non-responders. However, this difference is mainly caused by a deterioration of QoL in non-responders. Apparently, it is a matter of selection: the patients without a pain response are patients with a poorer QoL, both before and after treatment, and an observed shorter survival.(16, 24) The temporary decrease in physical health in the multiple fraction regimen we found in our current analyses, might be in line with some increase in fatigue the first two weeks after treatment, which was described in another paper, prospectively studying 518 patients. (9)

On the other hand, our results contradict several other studies, stating that radiation therapy leads to improvement of QoL. (9-13) However, these other studies have some limitations. For example, they only studied QoL at a limited amount of time points (10, 11, 13), focused on limited items (9, 12) or included small patient numbers (11). Moreover, statistically significant improvement of QoL does not necessary reflect clinically relevant improvement.

Although our study is based on a unique and large cohort of patients with bone metastases from the Netherlands, the data originate from the late nineties, which may be considered a limitation due to changes, in systemic and symptomatic treatments in the past years, which have altered the course of the disease. On the other hand, in the current paper we showed that, irrespective of survival, the pattern of QoL is similar in all patient groups. QoL remains stable for a long period and only deteriorates briefly before the end of life. Although the systemic treatment of patients with painful bone metastases and their survival has changed over time, the standard local treatment has remained palliative radiation therapy, with a single fraction of 8 Gy (3). Therefore, we believe these QoL results are still applicable to current patients with painful bone metastases. The RSCL and EORTC QLQ-C30 questionnaires that were used, are not specifically designed for patients with painful bone metastases. Therefore, small, but meaningful differences might have been missed by these global QoL questionnaires. For future studies, we would recommend using a bone metastases specific questionnaire, like the EORTC QLQ-BM22, which contains 22 questions, relevant to patients with bone metastases. Moreover, we would advise the EORTC PAL15 questionnaire instead of the C30. (25) Another possible limitation is that follow-up data may be biased, since patients with a good QoL and good performance status will be more likely to complete a questionnaire than patients in poor physical condition. However, since 74% of the patients died during follow up, we believe that the results towards death provide a meaningful outcome. A final shortcoming might be that we did not study patients with painful bone metastases who did not receive radiation therapy. Therefore, we cannot determine whether the stabilization of QoL is a benefit of treatment, although it seems reasonable to conclude that without treatment QoL would have deteriorated sooner.

Conclusion

Although radiation therapy for painful bone metastases often leads to a meaningful pain response, most domains of QoL do not improve after treatment. Only psychosocial QoL improves slightly after treatment. The level of QoL is related to the actual survival, with a rather stable course of QoL for most of the remaining survival time and afterwards a sharp decrease, starting several weeks before the end of life. For most QoL domains, a high pain score and intake of opioids are associated with worse QoL. A poor performance score is

associated with worse functional QoL. There is no difference in QoL between patients receiving a single fraction of 8 Gray and six fractions of 4 Gray, except for a temporary worsening of physical QoL after 6 fractions, up to four weeks after start of treatment.

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6

Quality of life in relation to pain response to radiation therapy for painful bone metastases

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Abstract

Purpose: To study quality of life (QoL) in responders and nonresponders after radiation therapy for painful bone metastases; and to identify factors predictive for a pain response.
Methods: The prospectively collected data of 956 patients with breast, prostate, and lung cancer within the Dutch Bone Metastasis Study were used. These patients, irradiated for painful bone metastases, rated pain, QoL and overall health at baseline and weekly afterward for twelve weeks. Using generalized estimating equations analysis, the course of QoL was studied, adjusted for primary tumor. To identify predictive variables, proportional hazard analyses were performed, taking into account death as a competing risk, and C-statistics were calculated for discriminative value.
Results: In total, 722 (76%) patients responded to radiation therapy. During follow-up, responders had a better QoL in all domains compared with nonresponders. Patients with breast or prostate cancer had a better QoL than patients with lung cancer. In multivariate analysis, baseline predictors for a pain response were breast or prostate cancer as primary tumor, younger age, good performance status, absence of visceral metastases, and using opioids. The discriminative ability of the model was low (C-statistic: 0.56).
Conclusions: Responding patients show a better QoL after radiation therapy for painful bone metastases than nonresponders. Our model did not have enough discriminative power to predict which patients are likely to respond to radiation therapy. Therefore, radiation therapy should be offered to all patients with painful bone metastases, aiming to decrease pain and improve QoL.

Introduction

Radiation therapy, with a single fraction of 8 Gray (Gy), is an effective treatment for patients with painful bone metastases, with a durable pain response rate of more than 60%. (1-3) Since painful bone metastases have a major impact on quality of life (QoL) in patients with advanced cancer (4, 5), reducing pain is likely to improve QoL. Although a few studies showed that radiation therapy for painful bone metastases contributes to improvement of QoL, no thorough studies have been published focusing on the course of QoL after radiation therapy. (4, 6-8) These patients frequently have other contributing factors that influence QoL, like visceral metastases, deteriorating physical condition, psychosocial issues or side-effects from systemic treatments. (4, 9) Furthermore, adequate treatment of pain at one site might unmask pain at other sites, resulting in migrating pain. As a consequence, it is unsure to what extent a response to palliative radiation therapy leads to improvement of QoL. To determine the effect of palliative radiation therapy for painful bone metastases on QoL, it is relevant to study the difference in QoL between responding patients and nonresponding patients. To our knowledge only one publication compared QoL in 22 responding patients versus 8 nonresponders. (8)

Moreover, it would be helpful to identify the remaining 30-40% of patients who will not respond to radiation therapy, in order to prevent overtreatment and loss of valuable time. These patients might benefit more from a change in pain medication (10) or other treatments, such as radiopharmaceuticals (11), bisphosphonates (12, 13), minimally invasive surgery (14, 15) and/or systemic therapy. In addition, psychological interventions might be helpful, using pain education or other supportive measures (16). Several studies have tried to identify factors predictive for pain response after palliative radiation therapy, like primary tumor type, radiographic imaging features, size of radiation therapy fields and baseline pain score. (17-23) However, the results are inconsistent, probably related to the small number and selection of patients and the variables studied. A validated predictive model for response to radiation therapy for painful bone metastases has not been published yet. The aim of the present study is to study the course of QoL in responding versus non-responding patients, who received radiation therapy for painful bone metastases within the randomized Dutch Bone Metastasis Study (DBMS). In this study, in 1157 patients, no differences in pain response were seen between a single fraction of 8 Gy and six fractions of 4 Gy. (1, 24, 25) A second objective of the present study was to assess the value of prognostic factors to predict a pain response after radiation therapy in patients with painful bone metastases.

Patients and methods

The DBMS was a nationwide, randomized controlled trial in patients with painful bone metastases. From 1996 to 1998, 1157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or 24 Gy in six fractions, in 17 out of the 21 radiation therapy institutions in the Netherlands. The main endpoint was pain response. Single and multiple fraction schedules were equally effective in reducing pain, with a pain response in 73-75% of patients and no specific patient subgroups benefitting from the higher total dose. (1, 24-27) Detailed descriptions of the study protocol have been published previously. (1, 28) The Medical Ethics Committees of all participating institutions approved the study. All patients provided informed consent. In December 1998, the database was updated for survival and closed.

Study population

For the present analyses, patients were grouped into three groups of the most common tumor sites: breast cancer, prostate cancer and lung cancer, with a total of 1005 patients. The remaining group of 152 patients had a variety of primary tumors, mainly bladder, colorectal, esophageal cancer and unknown primary tumor. We considered this group too heterogeneous, while the outcome would not be easily translatable into daily clinical practice. Therefore, we excluded those patients from the present analysis.

Scales

At randomization and during follow-up, patients filled out weekly questionnaires for twelve weeks and monthly thereafter until two years of follow-up, death or closure of the study. At randomization, the treating physician rated the performance status using the Karnofsky performance score (KPS) (29). The questionnaires consisted of, among others, a pain scale, medication intake, the Rotterdam Symptom Checklist (RSCL) (30) and a visual analogue general health scale (VAS-gh). Pain was measured using an 11-point numeric rating scale, from 0 (no pain) to 10 (worst pain imaginable). A pain score of at least 2 was required to enter the study. (1, 28) The RSCL consists of three QoL-subscales (psychological distress, physical symptom distress and activity level impairment) and a scale for overall valuation of life (on a seven-point Likert-type scale) (VRS-vl). Sum scores were calculated in accordance with the RSCL manual. (30) All QoL-scores were standardized to the range of 0 to 100, 0 representing the best possible and 100 representing the worst possible condition. The VAS-gh was noted on a line from 0 (no complaints) to 100 (worst general health possible). In general, a difference of ten points on a 100 point scale is considered to be clinically relevant.

At baseline, the RSCL-domains, VRS-vl and VAS-gh were available in 97%, 97% and 96% of patients, respectively. After six weeks, those numbers were 75%, 73% and 73%, respectively. After twelve weeks, 61% of patients filled out each of those items. Responding patients

had a better compliance than nonresponders, at six weeks 42-45% of nonresponding patients filled out the items, versus 82-85% of responding patients. At twelve weeks after treatment, 79% of patients were alive. 816 patients (85%) completed all questionnaires up to 4 weeks before their death. So, therefore, most missing data is due to (approaching) death. Following international criteria (31), pain response was defined as a decrease in the initial pain score by at least two points, without analgesic increase, or an analgesic decrease without an increase in pain score. No fixed time interval from the date of randomization was applied. Response analysis was possible in 956 patients, because 49 patients (5%) did not return at least two successive follow-up pain scores, which was needed to determine response.

Statistical analysis

To compare the categorical variables at baseline, Chi-Square tests were used. Survival curves were estimated using the Kaplan Meier method and differences between curves were assessed with the log-rank test. For comparing the course of QoL-domains over time between responders and nonresponders, we used generalized estimating equations (GEE-measurements), a longitudinal data analysis technique. Since primary tumor type is related to the chance of a pain response, it might be a confounder. Therefore, the QoL analyses were adjusted for this factor.

Effects of the different variables on the prediction of response were quantified using proportional hazard analyses according to the method of Fine and Gray. (32) This method takes into account all type of events, without assuming independency between the time to each of those events, but the effect depends on the magnitude of the risk of other competing events.

The vast majority of responses (97%) appeared within twelve weeks after randomization. Therefore, we considered all deaths within those twelve weeks as competing risks.

On the basis of the literature and clinical experience, the following baseline variables were studied for their value in predicting response: primary tumor (breast, prostate or lung cancer), age (≤65 years or >65 years), KPS (≤ 60, 70-80 or 90-100), baseline pain score (2-4, 5-7 or 8-10), presence of visceral metastases (yes or no), concomitant systemic therapy (yes or no), baseline pain medication (no opioids or use of opioids), painful localization (extremities, spinal column, pelvis or other). We used single imputation method to impute missing values of KPS (in six patients) and pain score (in three patients) at baseline. Correlation between variables was assessed using Pearson's correlation coefficients in order to assess the risk of multicollinearity of the potential predictors. Gender was not included into the model, since gender and primary tumor were highly correlated (Pearson correlation coefficient of 0.8). In a prognostic study, variables that are not significant in univariate analyses, should not be excluded for multivariate analyses. (33) Therefore, we started with all preselected variables for the development of the predictive model. Subsequently, we eliminated the variables by backward selection with a threshold p-value

of 0.20, until the model fit decreased significantly. The chosen p-value of 0.20 intends to limit the loss of information and to select also weaker predictors, although at the cost of including 'noise' variables. (34) In the regression analyses per primary tumor, we studied the full model, except for localization, since the degrees of freedom were limited in this analysis. In the analysis per primary tumor, gender was only studied in patients with lung cancer, due to the abovementioned correlation in patients with breast and prostate cancer. Discrimination of the predictive models was assessed with the C-statistic. A C-statistic is a measure for the discriminative ability of the model to distinguish between patients with a pain response and patients without pain response. A C-statistic ranges between 0.5 and 1.0. A value of 0.5 means that the model is no better than chance, while a value of 1.0 means perfect discrimination. (35)

The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc, Cary, NC, USA). The Fine and Gray competing risks and the C-statistics were calculated in the R language environment for statistical computing, version 2.10 (freely available at http://cran.r-project.org).

Results

Pain response

In total, 722 (76%) of 956 patients experienced a pain response after treatment. Median time to response was 3 weeks.

Quality of life

At baseline, there was a statistically significant difference in activity level impairment and VAS-gh between responders and nonresponders. Baseline psychological distress, physical symptom distress and VRS-vl did not differ significantly between responders and non-responders. Figure 1 shows the course of QoL for responders and nonresponders during the first twelve weeks of follow-up. The curves differ significantly between responders and nonresponders, with a higher score (reflecting more complaints) for nonresponders in all QoL domains (all p-values <0.001). Psychological distress, physical symptom distress, VAS-gh and VRS-vl deteriorate in nonresponders but improve in responders. Activity level impairment remains rather stable in responders but deteriorates in nonresponders. Figure 1 shows that the differences were small in the first weeks after treatment, but increased with time, becoming clinically relevant.

For all QoL domains, patients with prostate cancer had significantly better scores than patients with lung cancer. The average difference over time ranged between 2.2 points in physical symptom distress (p= 0.03) and 11.3 in activity level impairment (p<0.0001). Patients with breast cancer had a significantly better QoL than patients with lung cancer with regard to physical symptom distress, VRS-vl and VAS-gh.

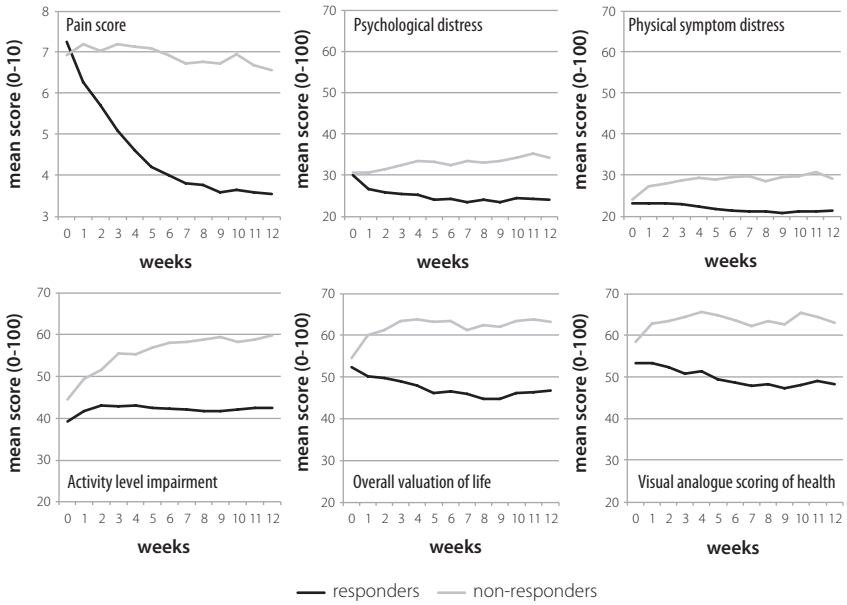

Figure 1 Course of pain and QoL in responders and nonresponders during twelve weeks after palliative radiation therapy. Dark line represents responders, grey line nonresponders. A higher score represents more complaints or a worse QoL.

Responders versus nonresponders

Table 1 shows the baseline characteristics of responding and nonresponding patients. No significant difference in response rate between the two treatment arms was noted. Of the patients with breast, prostate and lung cancer, 82%, 79% and 62% responded, respectively. Nonresponding patients more frequently had lung cancer and visceral metastases. The mean age differed significantly between responding and nonresponding patients: 64 years and 67 years respectively. Responding patients were in a better physical condition: 74% of responders had a pretreatment KPS of 70-100, compared to 64% of nonresponders. Patients with a KPS of 90-100, 70-80 and 20-60 responded in 84%, 76% and 69%, respectively. Baseline pain scores were comparable in responding and nonresponding patients. Nonresponders were less likely to receive systemic therapy prior to radiation therapy. Responding patients lived significantly longer than nonresponders: median survival was 35 weeks for the entire cohort, 16 weeks for nonresponders, and 45 weeks for responders ($p<0.001$). At closure of the study, 67% of responding patients and 87% of nonresponding patients had died.

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

baseline variables	pain response to radiotherapy			difference responders - nonresponders *
	all patients	*response*	*no response*	
n	956	722	234	
primary tumor				<0.001
breast	434	355 (82%)	79 (18%)	
prostate	253	200 (79%)	53 (21%)	
lung	269	167 (62%)	102 (38%)	
age (years)				0.009
≤ 65 years	463	367 (79%)	96 (21%)	
> 65 years	493	355 (72%)	138 (28%)	
gender				0.002
male	482	343 (71%)	139 (29%)	
female	474	379 (80%)	95 (20%)	
KPS				0.001
90 - 100	200	168 (84%)	32 (16%)	
70 - 80	488	370 (76%)	118 (24%)	
20 - 60	268	184 (69%)	84 (31%)	
pain score				0.762
2 - 4	198	152 (77%)	46 (23%)	
5 - 7	457	347 (76%)	110 (24%)	
8 - 10	301	223 (74%)	78 (26%)	
visceral metastases				0.04
no	722	557 (77%)	165 (23%)	
yes	234	165 (71%)	69 (29%)	
systemic therapy				<0.001
no	379	262 (69%)	117 (31%)	
yes	577	460 (80%)	117 (20%)	
treatment arm				0.525
1x8 Gy	483	369 (76%)	114 (24%)	
6x4 Gy	473	353 (75%)	120 (25%)	
pain medication				0.217
no opioids	556	428 (77%)	128 (23%)	
opioids	400	294 (74%)	106 (27%)	
painful localization				0.462
extremities	139	98 (71%)	41 (29%)	
spinal column	292	220 (75%)	72 (25%)	
pelvis	389	298 (77%)	91 (23%)	
other	136	106 (78%)	30 (22%)	

* : Pearson Chi-Square, KPS: Karnofsky performance score, Gy: Gray

Model

In total, 72 (8%) patients, who died within twelve weeks without experiencing a pain response, were considered as having a competing event.

Table 2 shows the results of the analyses of predictors for a pain response. The final model included primary tumor, age, Karnofsky performance score, presence of visceral metastases and use of opioids. The analysis showed that breast or prostate cancer, younger age, good performance status, no visceral metastases and opioids were associated with an increased chance of a pain response. However, the *C*-statistic of this final model was only 0.56, indicating low discriminative power. Table 3 shows the analysis of the predictors for a pain response per primary tumor. Only for breast cancer, two variables appeared to add to the prediction of a pain response, with a *C*-statistics of 0.55. The multivariate analysis in patients with breast cancer showed that younger age and no visceral metastases were associated with a higher chance of responding to radiation therapy. For patients with prostate or lung cancer, no additional predictors were identified.

Table 2 Analysis of factors predictive for a pain response to radiation therapy for painful bone metastases.

baseline variables	*% of patients with response*	*Hazard Ratio (95% CI)*	
		*UVA **	*MVA **
primary tumor			
breast	*355 (82%)*	1.00	1.00
prostate	*200 (79%)*	0.96 (0.82-1.11)	0.94 (0.79-1.11)
lung	*167 (62%)*	0.67 (0.56-0.79)	0.67 (0.56-0.81)
age			
≤ 65 years	*367 (79%)*	1.00	1.00
> 65 years	*355 (72%)*	0.86 (0.75-0.98)	0.88 (0.76-1.01)
KPS			
90 - 100	*168 (84%)*	1.00	1.00
70 - 80	*370 (76%)*	0.87 (0.75-1.02)	0.88 (0.75-1.03)
20 - 60	*184 (69%)*	0.78 (0.65-0.94)	0.81 (0.66-0.99)
pain score			
2 - 4	*152 (77%)*	1.00	*#*
5 - 7	*347 (76%)*	1.03 (0.87-1.21)	
8 - 10	*223 (74%)*	1.01 (0.84-1.21)	
visceral metastases			
no	*557 (77%)*	1.00	1.00
yes	*165 (71%)*	0.83 (0.70-0.97)	0.81 (0.69-0.96)
systemic therapy			
no	*262 (69%)*	1.00	*#*
yes	*460 (80%)*	1.22 (1.06-1.40)	
pain medication			
no opioids	*428 (77%)*	1.00	1.00
opioids	*294 (74%)*	0.99 (0.86-1.13)	1.12 (0.96-1.29)
painful localisation			
extremities	*98 (71%)*	1.00	*#*
spinal column	*220 (75%)*	1.14 (0.92-1.42)	
pelvis	*298 (77%)*	1.14 (0.93-1.41)	
other	*106 (78%)*	1.23 (0.95-1.58)	

95% CI : 95% confidence interval, UVA : univariate analysis, MVA : multivariate analysis, *: competing risk analysis according to Fine and Gray, KPS: Karnofsky performance score, # : did not remain in the final model

Table 3 Analysis of factors per primary tumor predictive for a pain response to radiation therapy for painful bone metastases.

baseline variables	primary tumor								
	breast			***prostate***			***lung***		
	patients with response n (%)	*Hazard Ratio (95% CI)*		*patients with response n (%)*	*Hazard Ratio (95% CI)*		*patients with response n (%)*	*Hazard Ratio (95% CI)*	
		*UVA **	*MVA **		*UVA **	*MVA **		*UVA **	*MVA **
age									
≤ 65 years	240 (85%)	1.00	1.00	48 (84%)	1.00	#	79 (65%)	1.00	#
> 65 years	115 (77%)	0.84 (0.69-1.03)	0.85 (0.69-1.04)	152 (78%)	0.87 (0.66-1.16)		88 (60%)	0.90 (0.68-1.18)	
gender	n.a.			n.a.					
male						#	140 (62%)	1.00	#
female							27 (63%)	1.14 (0.77-1.70)	
KPS									
90 - 100	85 (88%)	1.00	#	55 (86%)	1.00	#	28 (72%)	1.00	#
70 - 80	181 (81%)	0.93 (0.75-1.16)		106 (78%)	0.89 (0.68-1.18)		83 (64%)	0.80 (0.54-1.18)	
20 - 60	89 (78%)	0.92 (0.71-1.20)		39 (74%)	0.84 (0.58-1.21)		56 (55%)	0.68 (0.45-1.04)	
pain score									
2 - 4	76 (80%)	1.00	#	45 (83%)	1.00	#	31 (63%)	1.00	#
5 - 7	170 (84%)	1.15 (0.91-1.46)		93 (76%)	0.85 (0.62-1.16)		84 (64%)	1.08 (0.74-1.56)	
8 - 10	109 (80%)	1.10 (0.85-1.44)		62 (82%)	1.03 (0.74-1.45)		52 (59%)	0.92 (0.62-1.36)	
visceral metastases									
no	245 (84%)	1.00	1.00	194 (80%)	1.00	#	118 (62%)	1.00	#
yes	110 (77%)	0.77 (0.63-0.94)	0.77 (0.63-0.94)	6 (55%)	0.62 (0.26-1.48)		49 (61%)	0.98 (0.72-1.34)	
systemic therapy									
no	79 (85%)	1.00	#	39 (80%)	1.00	#	144 (61%)	1.00	#
yes	276 (81%)	0.89 (0.71-1.10)		161 (79%)	0.91 (0.66-1.26)		23 (72%)	1.27 (0.86-1.86)	
pain medication									
no opioids	236 (82%)	1.00	#	115 (77%)	1.00	#	77 (65%)	1.00	#
opioids	119 (82%)	1.11 (0.91-1.36)		85 (82%)	1.14 (0.89-1.46)		90 (60%)	0.92 (0.70-1.22)	

Abbreviations as in Tables 1 and 2. * : competing risk analysis, # : did not remain in the final model

Discussion

In the present analysis of the Dutch Bone Metastasis Study database on the effect of radiation therapy on QoL, we showed that response resulted in better QoL for all domains compared to non-response. Although the average differences were relatively small, the separating curves in figure 1 indicate a progressive clinically relevant difference between responding and nonresponding patients over time. Therefore, the average difference might not be the best measure to determine differences in QoL between responding and nonresponding patients.

The difference in QoL between responders and nonresponders was most outspoken in activity level impairment, VRS-vl and VAS-gh at 12 weeks. To our knowledge, only one small study in 59 patients has been published that compared QoL in 22 responders, 8 nonresponders and 29 patients with indeterminate response, using the QLQ-BM22 and the QLQ-C30. Even in such a small number of evaluable patients, they found significant differences after one month between responders and nonresponders in pain, painful site, painful characteristics, functional interference, physical functioning and role functioning. (8) Our results are in line with the studies by Cramarossa and by Wu, who found that less pain predicted for improved QoL, in patients receiving radiation therapy for painful bone metastases. (4, 7)

Secondly, we attempted to create a model to predict which patients with painful bone metastases are most likely to respond to palliative radiation therapy. Such a model, if predictive enough, might assist both clinicians and patients when choosing appropriate treatments for painful bone metastases. Despite the number of variables studied and the large number of included patients, the discriminative ability of the model was very low (C-statistic 0.56). Therefore, its clinical relevance is only minor.

Previous studies also tried to identify predictive factors for a favorable pain response after radiation therapy for painful bone metastases. In a non-randomized single center study from Italy in 205 patients, an effect of total dose and baseline performance score on pain response was found, with lower response rates in patients with lower doses and worse performance scores. (17) Other studies, all from a large research group in Canada, found no correlation between pain response and the size of the radiation field (18), computed tomography imaging features of spinal metastases (21), location within the spinal column or dose fractionation (22). They found no significant difference in response rate between 69 patients with bone metastases from gastrointestinal cancers and patients with bone metastases from other primary tumors. (19) Furthermore, they noticed no effect of painful localization, spinal versus non-spinal metastases, on response rate in 386 patients. (23) In a dataset of 1053 patients, they concluded that patients with mild/moderate pain at baseline had a comparable chance of having a pain response as patients with severe pain. At different time points after treatment, primary tumor was significantly related to the chance of having a pain response, with higher chances for prostate or breast cancer. (20)

Some of these studies have limitations, like assessing only one or two specific variables (18, 19, 23), including a small number of patients (19, 21, 22), retrospective collection of data (17) or not using state-of-the-art methods (33) for prognostic modeling (17). Although their joint results suggested that total radiation dose, performance status and primary tumor might be predictors for response, these studies did not present the discriminative ability of these variables using C-statistics or other similar statistical test outcomes. In our analyses, primary tumor and performance status were confirmed as variables predicting response. The study by Arcangeli et al., that concluded those variables to be predictors, was a non-randomized single center study in which 65% of patients received a dose above 30 Gy in at least ten fractions. (17) In addition, they only studied complete response in their multivariate analysis and the definition of response was not according to the more recent international criteria also taking into account changes in analgesic intake (31). In conclusion, the literature and our results do not consistently demonstrate any clear factors, other than primary tumor and performance status, predicting a pain response after radiation therapy for painful bone metastases.

Some methodological aspects of our present analysis require discussion. The Dutch Bone Metastasis Study dataset provides a unique insight in cancer patients receiving palliative radiation therapy, due to the large number of patients included and the frequency and contents of follow-up. A disadvantage of our database is that it contains no items on concomitant comorbidities or medication, which might also effect the course of QoL. The compliance in responders and nonresponders differed. GEE analysis was chosen to be the best statistical method, considering this difference. (36)

Although our data were collected from 1996 until 1998, we believe the characteristics and outcome after treatment of these patients are still representative for current patients receiving radiation therapy for painful bone metastases. While improvements, for example in systemic therapy have occurred over the last years, the most frequent applied treatment for painful bone metastases is still palliative radiation therapy, with a single fraction of 8 Gy as the golden standard. (3)

Conclusion

Patients responding to radiation therapy for painful bone metastases had a better QoL than nonresponders during the first three months after treatment. We were unable to develop a model to accurately predict pain response to radiation therapy. Therefore, since 76% of studied patients responded, radiation therapy should be offered to all patients with painful bone metastases, aiming to reduce their pain and consequently to improve their QoL.

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7

Effect of age on response to palliative radiotherapy and quality of life in patients with painful bone metastases

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Abstract

Background: Multimorbidity and declining performance in elderly cancer patients may result in less treatment benefit. We investigated whether age is a predictor for pain response and quality of life (QoL) after radiotherapy in patients with painful bone metastases.

Methods: The database of the Dutch Bone Metastasis Study was used (1996-1999). 1157 patients, irradiated for painful bone metastases, rated their pain, QoL-domains and overall health at baseline and during follow-up. Response was calculated taking into account changes in pain score and medication. Patients were grouped into three age cohorts: A: <65 (n=520), B: 65-74 (n=410) and C: ≥ 75 years (n=227).

Results: No significant difference existed in pain response between cohorts: 78% in cohort A, 74% in B and 67% in C. When assessing baseline QoL, a significant difference in activity level was noticed, with more impairment in elderly compared to younger patients (C versus B ($p=0.01$), C versus A ($p<0.001$)). Other QoL-domains were similar at baseline and during follow-up among cohorts. A pain response was significantly associated with improvement of health-related QoL (OR 3.74, 95% CI 2.66-5.25).

Conclusions: The majority of elderly patients with painful bone metastases responded to radiotherapy and showed comparable overall QoL compared to their younger counterparts. Age is not a predictor for pain response or QoL.

Introduction

The incidence of cancer increases with age. [1-3] Data from the last decades show that for the most common cancers, the percentage of patients aged 65 years and older is over 50%. [2] The number of elderly cancer patients is increasing due to a longer life expectancy, improved cancer treatments and increased tumor-specific survival. [2,3] Moreover, the aging of the babyboom era is coming. The number and proportion of elderly patients with cancer is thus expected to increase dramatically [3], with up to 42% of cancer patients in the United States in 2050 being 75 years and older. [2] Elderly patients with cancer represent a different and more fragile population than younger patients, with specific age-related problems and needs, related to multimorbidity and poorer physical or cognitive condition. They are frequently excluded from or underrepresented in clinical trials. [4] Therefore, trial outcomes and subsequent choices for medical treatments may not be applicable to this group. Studies show that elderly cancer patients receive different treatments than younger patients. [5-8] In both Canada and the United States, for example, elderly patients were less likely to be referred even for an effective palliative treatment such as radiotherapy. [9-11]
Painful bone metastases have a major impact on quality of life (QoL) of cancer patients. [12,13] Radiotherapy with a single fraction of 8 Gray (Gy) is considered the standard treatment for patients with painful bone metastases, with a pain response rate of more than 60%. [14-17] The Dutch Bone Metastasis Study (DBMS) is the largest trial contributing to these outcomes, with 1157 patients included. [14,17] Both single and multiple fraction schedules were equally effective in treating pain, with a pain response in 73-75% of patients and no specific patient subgroups benefitting from higher total doses. [14,17-20]
To determine whether palliative radiotherapy is justified in elderly patients with painful bone metastases, the DBMS database was used. We investigated whether age is a predictor for pain response and QoL after radiotherapy for painful bone metastases.

Patients and methods

The DBMS was a nationwide, randomized controlled trial in patients with painful bone metastases. From 1996 to 1998, 1157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or 24 Gy in six fractions. The main endpoint of the study was pain response. Detailed descriptions of the study protocol have been published previously. [14,17] The Medical Ethics Committees of all participating institutions approved the study. All patients provided informed consent.

Questionnaires

At randomization and during follow-up, patients filled out weekly questionnaires for twelve weeks and thereafter monthly until two years of follow-up, death or closure of the

study in December 1998. These questionnaires contained a pain scale, QoL-related questions from the Rotterdam Symptom Checklist (RSCL) [21], a visual analogue general health scale (VAS health) and medication intake.

Analyses

For the present analyses, we used the pain scale, QoL scores of the RSCL and VAS health for twelve weeks after randomization. This time frame was chosen to limit the influence from tumor progression or other treatments. To study the effect of age, patients were grouped into three age cohorts: A: patients under 65 years, B: 65 to 74 years and C: 75 years and older.

Pain response analyses

Pain was measured on an 11-point numeric rating scale, from 0 (no pain) to 10 (worst pain imaginable). Following international criteria [22], pain response was defined as a decrease in the initial pain score by at least two points, without analgesic increase, or analgesic decrease without an increase in pain score. No fixed time interval from the date of randomization was applied. A response was calculated if at least two successive follow-up pain scores were available. Response analysis was possible in 1099 patients, because 58 patients (5%) did not return enough questionnaires to determine response.

Quality of life analyses

The RSCL consists of three QoL-subscales (psychological distress, physical symptom distress and activity level impairment, on a four-point Likert-type scale) and a scale for overall validation of life (on a seven-point Likert-type scale). [21] Sum scores were calculated in accordance with the manual of the RSCL. [21] We reversed the scores of activity level impairment, with a high score indicating a high level of impairment. All QoL-scores were standardized to the range of 0 to 100, with 0 representing the best possible and 100 representing the worst possible condition. The VAS health was noted by patients on a line from 0 to 100, with 100 representing a poor general health situation. At baseline, the RSCL-domains, overall validation of life and VAS health were available in 94%, 94% and 92% of patients, respectively.

To assess the effect of palliative radiotherapy on health-related QoL, we compared the VAS health eight weeks after treatment with the VAS health at baseline. If this score was missing at eight weeks, we used the previous score at week seven or six. This time period was chosen because by then most responders had already noticed the effect of treatment, while possible transient side-effects had passed. Any decrease in VAS health, compared to baseline, was considered an improvement of QoL. If patients did not return their questionnaire or died within eight weeks after treatment, this was considered a deterioration of QoL.

Statistical analysis

The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc, Cary, NC, USA).

For the categorical variables at baseline, Chi-Square tests were used. For continuous variables we used the one-way ANOVA, with Bonferroni post-hoc testing. Correlation between variables was studied using Pearson's correlation coefficients. To assess survival, we used Kaplan Meier method with a log-rank test. P-values are based on 2-sided tests and considered significant if $p<0.05$. To identify which variables predicted pain response and in particular to determine whether age is a predictor, Cox proportional hazard models were used. The preselected baseline variables, based on literature and clinical knowledge, were age (cohorts A/B/C), gender (male/female), Karnofsky performance score (KPS) [23] (90-100/70-80/≤ 60), pain score (2-4/5-7/8-10), primary tumor (breast/prostate/lung cancer/other types), presence of visceral metastases (yes/no) and concomitant systemic therapy (yes/no). The full model contained all preselected variables. Subsequently, we eliminated the variables by backward selection with a threshold p-value of 0.20, until the model fit decreased significantly. The chosen p-value of 0.20 intends to limit the loss of information and to select also weaker predictors, although at the cost of including 'noise' variables. [24]

For comparing the course of the QoL-domains over time between age cohorts, we used generalized estimating equations (GEE-measurements), a longitudinal data analysis technique. In all models, the outcome variables (RSCL-subscales and VAS health) were analyzed as a dependent variable using age cohort as a key independent variable. To identify predictors of improvement of health-related QoL (dichotomized into yes or no) and to determine whether age is a predictor, logistic regression was used. All preselected variables (at baseline: age, primary tumor, pain score, visceral metastases, gender, KPS and systemic therapy and during follow-up: pain response (yes/no)) were analyzed with a backward selection process with a threshold p-value of 0.20.

Results

Patient characteristics

Table 1 shows patient characteristics by age cohort. The mean age was 65 years (range 32 – 89 years). Cohort A (<65 years) consisted of 520 patients (45%), B (65-74 years) of 410 patients (35%) and C (≥75 years) of 227 patients (20%). There were significant differences in gender and primary tumor between age cohorts. Patients older than 64 years were more likely to be male and to have prostate cancer, while patients in cohort A were more often females with breast cancer. At baseline, there were significant age differences in KPS ($p = 0.004$), the percentage of patients with KPS 20-60 being 26% in cohort A, 29% in cohort B and 39% in cohort C. Baseline pain scores were not significantly different between cohorts. Visceral metastases were more frequently present in patients younger than 65

years: 35% in cohort A compared to 24% in cohort B (p<0.001) and 17% in cohort C (p<0.001). Younger patients lived significantly longer than elderly patients: median survival was 35 weeks (cohort A), 27 weeks (B) and 27 weeks (C) respectively (p=0.047).

Pain response

The overall pain response rate was 74%. Response was not significantly different between age cohorts: 78% in A versus 74% in B (p=0.42) and 67% in C (p=0.07). Mean time to response did not differ between cohorts (A: 3.6 weeks, B: 3.8 weeks, C: 3.1 weeks). Table 2 shows the results of the analysis of predictors for pain response. The final model included primary tumor and visceral metastases and showed that having breast cancer and the absence of visceral metastases were associated with an increased chance of pain response. Age was not an independent predictive factor for pain response. When analyzed per fractionation schedule, both models eliminated age as a predictor.

Quality of life

At baseline, activity level impairment was significantly different between age cohorts: mean score 48.6 in cohort C compared to 40.9 in B ($p = 0.01$) and 37.5 in A ($p < 0.001$). The other QoL subscales did not differ significantly between age cohorts. Figure 1 shows the course of QoL for age cohorts. These curves were largely superimposable, with a slight, statistically significant, but clinically irrelevant improvement over time, except for mean activity level impairment. GEE analysis showed a significant difference in the course of activity level impairment between the youngest cohort (A) and the oldest cohort (C) ($p < 0.001$) and between cohort B and C ($p = 0.0032$) (Figure 1). Table 3 lists the factors predictive for improvement of health-related QoL. The final model included pain response, primary tumor, visceral metastases and KPS. Having a pain response was predictive for improvement of health-related QoL. Patients with breast cancer or prostate cancer more frequently had improvement than those with lung cancer and other tumors. No difference was seen between age cohorts in terms of improvement of health-related QoL.

Table 1 Baseline characteristics for the three age cohorts (**A**: <65 years, **B**: 65-74 years, **C**: ≥ 75 years) of patients included in the Dutch Bone Metastasis Study (n=1157).

	age cohort			p-value [a]	difference between cohorts [b]
	A	**B**	**C**		
	< 65 yrs	*65-74 yrs*	*≥ 75 yrs*		
n	520	410	227		
gender				< 0.001	
male	198 (38%)	267 (65%)	159 (70%)		A-B (p < 0.001)
female	322 (62%)	143 (35%)	68 (30%)		A-C (p < 0.001)
Karnofsky performance score				0.004 [c]	
90 - 100	102 (20%)	85 (21%)	34 (15%)		A-C (p = 0.001)
70 - 80	283 (54%)	203 (50%)	101 (45%)		B-C (p = 0.021)
20 - 60	134 (26%)	120 (29%)	89 (39%)		
pain score				n.s. [c]	
2 - 4	105 (20%)	91 (22%)	38 (17%)		
5 - 7	231 (44%)	202 (49%)	117 (52%)		
8 - 10	184 (35%)	115 (28%)	71 (31%)		
primary tumor				< 0.001	
breast cancer	277 (53%)	115 (28%)	59 (26%)		A-C (p < 0.001)
prostate cancer	49 (9%)	123 (30%)	95 (42%)		B-C (p = 0.009)
lung cancer	117 (23%)	124 (30%)	46 (20%)		
other	77 (15%)	48 (12%)	27 (12%)		
visceral metastases				< 0.001	
no	337 (65%)	313 (76%)	188 (83%)		A-B (p < 0.001)
yes	183 (35%)	97 (24%)	39 (17%)		A-C (p < 0.001)
systemic therapy				n.s.	
no	232 (45%)	203 (50%)	96 (42%)		
yes	288 (55%)	207 (51%)	131 (58%)		
treatment schedule				n.s.	
1 x 8 Gy	257 (49%)	206 (50%)	118 (52%)		
6 x 4 Gy	263 (51%)	204 (50%)	109 (48%)		

Gy : Gray, n.s. : not significant, [a] Pearson Chi-Square, [b] non-significant differences are not shown, [c] also tested as a continuous variable, using one-way ANOVA and Bonferroni post-hoc testing

Table 2 Univariate (UVA) and final multivariate (MVA) Cox regression analysis on potential baseline predictors for pain response to palliative radiotherapy in patients with painful bone metastases.

baseline variables	% of patients with response	Hazard Ratio (95% CI)	
		UVA [a]	Final MVA [a]
age			
< 65 years	78%	1.00	[b]
65-74 years	74%	0.94 (0.81-1.10)	
≥ 75 years	67%	0.84 (0.69-1.02)	
gender			
male	70%	1.00	[b]
female	79%	1.14 (1.00-1.31)	
Karnofsky performance score			
90 - 100	82%	1.00	[b]
70 - 80	75%	0.93 (0.78-1.11)	
20 - 60	68%	0.91 (0.74-1.11)	
pain score			
2 - 4	75%	1.00	[b]
5 - 7	73%	1.01 (0.84-1.21)	
8 - 10	74%	1.09 (0.90-1.33)	
primary tumor			
breast cancer	82%	1.00	1.00
prostate cancer	79%	0.96 (0.81-1.14)	0.92 (0.77-1.10)
lung cancer	62%	0.76 (0.63-0.91)	0.74 (0.62-0.90)
other	64%	0.71 (0.56-0.89)	0.72 (0.57-0.91)
visceral metastases			
no	76%	1.00	1.00
yes	69%	0.87 (0.74-1.02)	0.88 (0.74-1.03)
systemic therapy			
no	68%	1.00	[b]
yes	79%	1.16 (1.01-1.33)	

95% CI : 95% confidence interval, UVA : univariate analysis, MVA : multivariate analysis,
[a] Cox regression analysis, [b] did not remain in the final model
MVA: the full model contained all variables. We eliminated the variables by backward selection, with a threshold p-value of 0.20, until the model fit decreased significantly and the final model remained.

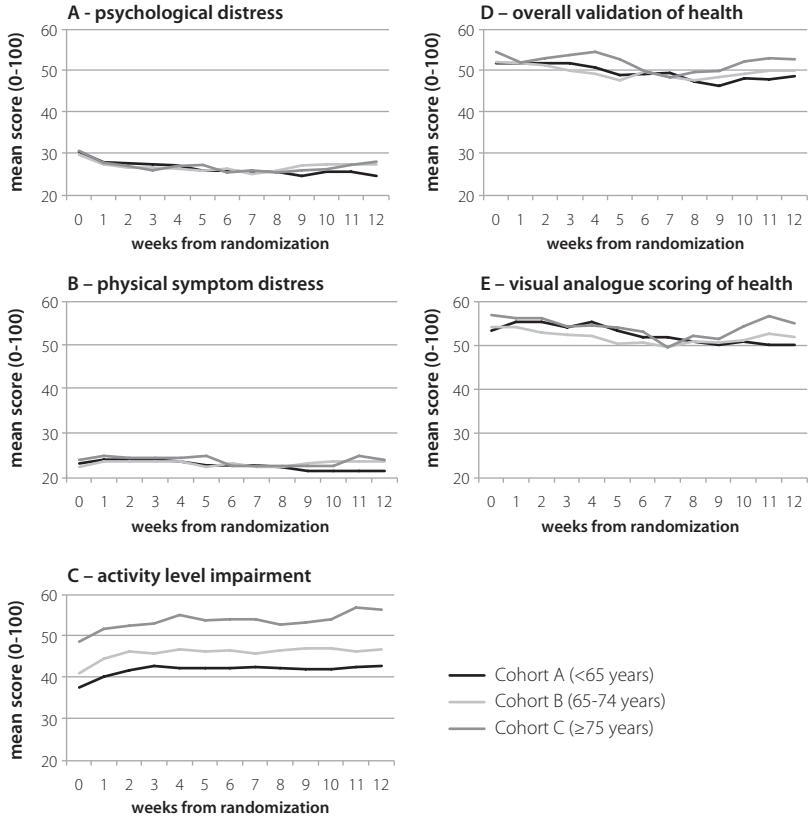

Figure 1 Quality of life in the first twelve weeks after palliative radiotherapy. On the X-axis week numbers, week 0 indicating baseline, number 1 the first week after treatment et cetera. All scores range from 0-100, with 100 indicating maximum amount of complaints.

Table 3 Univariate (UVA) and final multivariate (MVA) logistic regression analysis of potential predictive variables for improvement of health-related quality of life (defined by VAS health) six to eight weeks after radiotherapy.

baseline variables	% of patients with improvement of VAS health	Odds Ratio (95% CI)	
		UVA [a]	Final MVA [a]
age			
< 65 years	39%	1.00	[b]
65-74 years	39%	0.98 (0.75-1.28)	
≥ 75 years	36%	0.87 (0.63-1.20)	
gender			
male	35%	1.00	[b]
female	43%	1.41 (1.11-1.79)	
Karnofsky performance score			
90 - 100	37%	1.00	1.00
70 - 80	41%	1.22 (0.89-1.68)	1.52 (1.08-2.13)
20 - 60	34%	0.88 (0.62-1.26)	1.31 (0.90-1.92)
pain score			
2 - 4	39%	1.00	[b]
5 - 7	38%	0.97 (0.71-1.32)	
8 - 10	39%	1.03 (0.73-1.44)	
primary tumor			
breast cancer	46%	1.00	1.00
prostate cancer	44%	0.93 (0.68-1.25)	0.90 (0.64-1.25)
lung cancer	25%	0.38 (0.28-0.53)	0.46 (0.33-0.66)
other	30%	0.49 (0.33-0.73)	0.59 (0.39-0.90)
visceral metastases			
no	41%	1.00	1.00
yes	32%	0.68 (0.51-0.89)	0.74 (0.55-1.01)
systemic therapy			
no	31%	1.00	[b]
yes	44%	1.78 (1.38-2.24)	
pain response			
no	18%	1.00	1.00
yes	48%	4.08 (2.93-5.68)	3.74 (2.66-5.25)

95% CI : 95% confidence interval, UVA : univariate analysis, MVA : multivariate analysis,
[a] logistic regression analysis, [b] did not remain in the final model
MVA: the full model contained all variables. We eliminated the variables by backward selection, with a threshold p-value of 0.20, until the model fit decreased significantly and the final model remained.

Discussion

The present analyses of the DBMS database show that 67% of elderly patients (≥ 75 years) with painful bone metastases respond to palliative radiotherapy. Our study showed an 11% lower response rate in the elderly cohort. This difference did not reach statistical significance at a level of p≤ 0.05. In multivariate analysis, age was not an independent predictive factor for pain response or QoL after radiotherapy. Even if multivariate analysis would have shown age to be a predictor of pain response, there would still be no reason to treat elderly patients differently and to withhold palliative radiotherapy. Our results are in line with the outcomes of Campos et al, showing response to palliative radiotherapy for painful bone metastases to be independent of age. [25] These outcomes are important, since cancer disproportionally strikes elderly. [2,3] However, several studies show that elderly frequently receive different medical treatments than younger patients [5-11], because of fear of higher toxicity and expected lower effectiveness. Moreover, our analysis shows that pain response is an important factor leading to improvement of QoL. Caissie et al. prospectively studied the course of QoL in 178 patients treated with radiotherapy for painful bone metastases. They also showed pain response is associated with improvement of QoL. [26]

In the literature, inconsistent results concerning QoL in elderly patients with cancer have been reported. [27-29] One could argue their QoL is less than that of younger cancer patients, because of multimorbidity, increased physical and/or mental impairment [25,28] or diminished social support networks [29]. On the other hand, they might be better able to cope with their limitations than younger people, because of life experience and different expectations of remaining life, resulting in an equal or better QoL. [27,30] Our study supports the latter thought, with only a difference in activity level impairment between elderly and younger patients and equivalent other QoL-scores.

In our study population, 39% of the patients aged 75 years or older had a KPS of ≤ 60 against 26% of the patients under 65 years. A difference in performance status between elderly and younger patients was also seen in a study by Campos. [25] In a population of 558 patients who received radiotherapy for painful bone metastases, they showed that younger patients had higher KPS. Remarkably, our study shows patients with a lower KPS (<70) had a comparable pain response and improvement of QoL compared to patients with a higher KPS. So a lower KPS should not be a reason to restrain palliative radiotherapy, even if patients are elderly. Since KPS is associated with activity level impairment, the lower performance status in the elderly cohort is probably reflected in the difference we found in activity level impairment.

In order to study QoL in elderly patients with cancer, a separate EORTC-QLQ-ELD15 questionnaire has been developed. [31] When patients were asked what items they thought to be important and relevant, elderly people considered mobility to be more important and relevant than younger patients. [31] It is therefore most important that our data show

that, despite more activity level impairment, elderly patients did not evaluate their overall QoL different compared to younger patients. The aforementioned life experience and adjusted expectations might enable those elderly to cope more easily with limitations without lowering overall valuation of life.

Some methodological aspects of our study require discussion.

Our choice for division in age cohorts is arbitrary. The literature shows different cut-offs in defining the elderly population. [31,32] Because in The Netherlands 65 years was, at the time of the study, the age people retired from work, cohort A represents the potentially working population. Patients aged 75 years and older are separated because of increased multimorbidity and frailty.

This dataset provides a unique insight in cancer patients receiving palliative care, due to the number of patients included, the percentage of elderly and the frequency and contents of follow-up. Although our data were collected from 1996 until 1998, we believe these patients are still representative for current patients receiving palliative cancer care. While improvements in systemic therapy have occurred over the last years, the most frequent applied treatment for painful bone metastases is still palliative radiotherapy, with a single fraction of 8 Gy as the golden standard. [16] This analysis provides no reason to treat elderly differently. One could argue that the aforementioned improvements in systemic therapies might also affect QoL. However, although almost half of the patients in our population received systemic therapy at randomization, systemic therapy was not an independent prognostic factor for pain response or improvement of QoL.

Conclusion

The majority of elderly patients showed a meaningful pain response to radiotherapy. Response to palliative radiotherapy leaded to improvement of QoL. Age was not a predictor for pain response or QoL. Elderly patients did not evaluate their overall QoL inferior compared to younger patients. Therefore, higher age should not be a reason to withhold palliative radiotherapy. In view of the increasing proportion of elderly patients in palliative care and the underrepresentation in clinical trials, future studies should focus on elderly patients with cancer.

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8

Discussion and future perspectives

The research in this thesis focuses on several aspects of quality of life in patients with painful bone metastases who were treated with palliative radiotherapy. Knowledge of quality of life, in relation to radiotherapy and the natural course of the disease, is important for patients and physicians. It impacts decision making and personalization of treatment. Research questions we tried to answer in this thesis involve estimation of survival, side-effects of radiotherapy, course of quality of life after radiotherapy, both in general and related to a pain response, and the effect of age on a pain response.

Impact of the Dutch Bone Metastasis Study on knowledge about bone metastases

For the analyses presented in this thesis, we used the data of the Dutch Bone Metastasis Study (DBMS), a study that included 1157 patients with painful bone metastases between 1996 and 1998 and randomized between a single fraction of 8 Gray (Gy) and six fractions of 4 Gy. (1,2) The first analyses of this study have led to an important increase of knowledge worldwide about effectiveness of radiotherapy, in general, but also in long and short survivors. Furthermore, papers were published studying cost-effectiveness, factors influencing retreatment, assessment of the fracture risk, survival prediction in patients with vertebral metastases and health care utilization in the palliative phase. (1-9)
For the further analyses presented in this thesis, we again used this dataset because of its largeness and uniqueness, with follow-up data on pain, quality of life (QoL) items and side effects. The main outcome of the DBMS, that a single fraction of 8 Gy is as good as a treatment schedule with multiple fractions in terms of pain relief, was confirmed by many other, but smaller, randomized studies, all published between 1986 and 2009. Several meta-analyses were performed, all confirming that there is no dose-response effect in radiotherapy for uncomplicated painful bone metastases (figure below). (10-13)
Therefore, the golden standard in treating patients with painful bone metastases, is a single fraction of 8 Gy. In 2014 the results of a large randomized trial in patients re-irradiated for painful bone metastases, were published. This trial demonstrated non-inferiority of a single fraction of 8 Gy compared to multiple fractions in terms of a pain response in previously treated patients. (14) As a consequence, a single fraction of 8 Gy is also the standard in retreatment.

Durability of DBMS outcomes

A comment on the durability of the outcomes of the DBMS could be that changes in systemic anticancer therapies and the widespread introduction of bone modifying agents such as zoledronic acid have occurred over the years. These changes should be reflected in survival times. In one of the studies in this thesis, we validated our prognostic survival

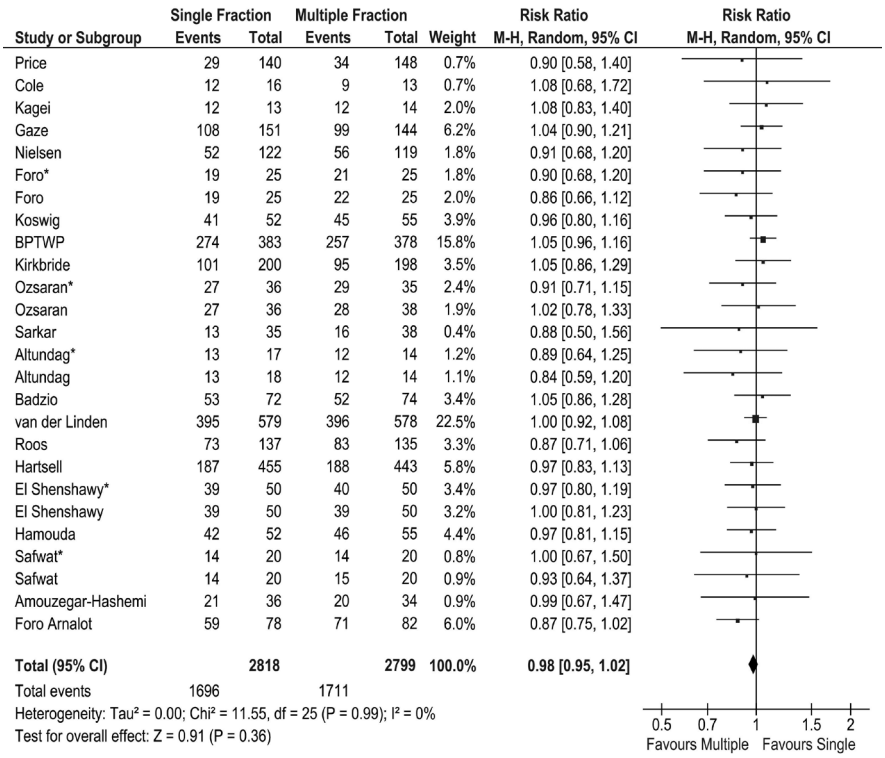

Figure 1 Overall response rates for single versus multiple fractions for intention-to-treat patients.

Source: Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. Clin Oncol (R Coll Radiol) 2012 Mar;24(2):112-124.Used with permission.

model with a more recent cohort of patients, treated between 2001 and 2010. It shows that survival times have not improved dramatically in the meantime. Furthermore, little is known about the effect of systemic treatments on pain in patients with painful bone metastases. In patients with metastatic prostate cancer, the effect of systemic treatment on pain has been reported in several studies. For example for docetaxel, a reduction in pain has been documented. (15) For cabazitaxel and mitoxantrone improvement of pain in less than 20% of patients was noted, while pain worsened in more than 30% of patients, after a median follow-up of 25 months. (16) A relatively new therapy for patients with breast cancer with bone metastases, is trastuzumab. To our knowledge, no data on pain response are known, since pain and analgesic use are not routinely assessed in trials involving trastuzumab. A French study included 128 patients with at least three-year

progression free metastatic breast cancer after using trastuzumab, therefore representing a favorable subset of patients. Of those 128 patients, 43% had initial bone metastases and the study showed bony disease progression in 24% of cases, without data on pain. (17) Although no comparative studies are available, radiotherapy seems to have more effect on pain due to bone metastases than systemic therapy. To our knowledge, no data exist that suggests that current systemic treatments have more effect on pain than the systemic treatments in the era of the DBMS.

Synchronizing methodology of trials

In research related to the treatment of bone metastases, using similar endpoints is important, in terms of pain response and other outcomes. Therefore, in 2000 an International Bone Metastases Consensus Working Party on endpoint measurements was established, with the purpose to define an international consensus on endpoints and to formulate remaining questions. In 2002 the consensus was published, with an update in 2012. These endpoints take into account both pain scores and pain medication, in determining a pain response. Furthermore, advices on re-irradiation timing, use of questionnaires, follow-up, pain measurement, analgesic treatment et cetera are given in this consensus. (18,19) Those endpoints and recommendations should be followed for future trials in patients with painful bone metastases, for all treatment modalities, to define the real effect of treatment without the influence of changes in pain medication. Furthermore, it will simplify comparison between trials and treatment modalities. Since the first international consensus agreement was published after the initial publication of the DBMS (2), in 2004 a further analysis was published, using those international standards in terms of pain response and taking into account the effect of retreatment. (1) Unfortunately, many trials do not follow those international endpoints, making it difficult to compare the trials and determine which treatment modality is better in terms of pain response than others.

Prognostic models

More and more, also in palliative settings, prognostic models are developed in order to help patients and their caregivers to balance treatment options and to individualize treatment by weighing benefits and disadvantages. These models should have prognostic accuracy, validation in a different dataset and calibration and discrimination should be evaluated. (20,21) In addition, simplicity of those tools is preferred, in order to be feasible in daily clinical practice. Regrettably, in palliative care, many models exist that have not been properly tested, hampering use in clinical practice. As a result, those models might even guide decision making in the wrong direction. Thus, when a treatment decision

depends on or is influenced by a model, physicians should ensure themselves that the model has sufficient predictive power and that is has been developed in accordance with methodological guidelines. (20) Unfortunately, this subject is not yet covered in the most recent consensus of the IBMCWP, but will hopefully be discussed in the following update. Current models mainly predict outcomes like survival, risk of fracture and chance of response. In the future, further attention should be paid to models predicting outcomes like QoL or patient-related outcome measurements (PROMs). Nevertheless, due to the importance and the increase in use of these models, critical use of prognostic models should be covered in the education programs of oncologists, general practitioners and other physicians.

Important outcomes of this thesis

Survival

An adequate estimation of survival is important for both patients and physicians to carefully weigh the time and effort needed to achieve treatment effect against the remaining survival time. In chapter 2, we developed an easy tool to predict survival of patients with painful bone metastases, and validated the model in a different, more recent cohort. (22) These two datasets from different treatment periods show that, despite changes in systemic treatment, survival times have only improved for patients with bone metastases of breast cancer and prostate cancer who are in a good clinical condition. Our goal was to facilitate physicians to estimate survival time for their individual patient, which may help patients and physicians in deciding about different treatment options, like radiotherapy or more invasive (such as surgery) or time consuming (such as stereotactic radiotherapy) treatments. In order to make the tool usable for daily clinical practice, we determined the predictive value of variables that are easily obtained in daily clinical practice. Our data show that the median survival of patients with a Karnofsky Performance Status below sixty, with other primary tumors than breast or prostate cancer, is roughly two months. Since mean time to response is three to four weeks (1), treatment of these specific patients is doubtful. This model can guide daily clinical decision making, despite not being highly accurate. Hopefully, in the future, more accurate and simple models will be developed helping physicians and their patients in providing adequate palliative care.

Quality of life (QoL)

Health-related QoL is defined as a multidimensional construct encompassing perceptions of both positive and negative aspects of physical, emotional, cognitive and social functions, due to the sequelae of a disease and its treatment. (23) Palliative care should focus on improving QoL by preventing or relieving suffering by assessing and treating pain and other problems, physical, psychosocial and spiritual. (24) Since painful bone

metastases have a negative impact on the overall QoL of patients (25,26), treatment may improve or at least maintain QoL. Still, the expected treatment effect on QoL should be taken into account when deciding about treatment in the palliative phase.

QoL after radiotherapy

Few studies have been published about the course of QoL after palliative radiotherapy, with a limited amount of data and follow-up. (27) Being aware of the expected course of QoL is important for both patients and physicians, to avoid incorrect expectations and to assist in treatment decisions. In chapter 5, we studied QoL after radiotherapy for painful bone metastases. We noticed a pattern with a rather stable level of QoL, regardless of survival time, deteriorating shortly before death.

A review of the available literature showed that patients who experienced a pain response also reported improvement of QoL. (27) Since QoL is a multidimensional concept (23), one could on the other hand imagine that a response to palliative radiotherapy does not impact QoL very much, since other complaints might appear and mainly the physical dimension of QoL is affected by reducing pain. Secondly, since many patients have multiple bone metastases, a shift in pain might appear when one site of metastases is treated. In chapter 6, we studied QoL after radiotherapy in relation to a pain response, using the Rotterdam Symptom Checklist (28). During follow-up we noticed that responding patients had a better QoL than non-responding patients, for all domains of QoL. In general, QoL of responding patients improved after treatment, although the difference was less than ten points on a 0-100 scale, indicating little clinical significance. QoL of non-responding patients further declined after treatment, causing an increasing difference in QoL between both groups.

The questionnaires used (the RSCL and two questions from the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of life Questionnaire (QLQ)-C30 (29)) are not specifically developed for patients with bone metastases. With more specific questionnaires, such as the later developed EORTC QLQ-Bone Metastases 22 (BM22) (30), larger differences in QoL might have been found. For future trials, we would recommend using the EORTC-QLQ-BM22.

We also tried to identify those patients who were likely to experience a pain response after treatment. The predictive accuracy of the final predictive model, consisting of five variables (primary tumor, age, performance status, visceral metastases and the use of opioids), was very low, with a C-statistic of 0.56. Thus, the minority of patients who do not respond to radiotherapy cannot reliably be predicted beforehand. All patients with painful bone metastases should therefore be considered for palliative radiotherapy, of course taking into account the expected survival as mentioned before. It is however important to discuss the expected outcome with patients, to make sure they can weigh for themselves the expected effect and the disadvantages. Patients are nevertheless often motivated to undergo every possible treatment, but it is the physician's duty to determine whether this

is justified. For example a rapidly declining performance status can be a sign that the end of life is near. In general, when survival is estimated less than one month, radiotherapy should not be considered. This is often the case in patients with a different primary tumor than breast or prostate cancer, who are no longer able to fully take care of themselves.

QoL in elderly patients

The population of cancer patients is ageing (31,32). Studies show that elderly patients are less likely to receive palliative radiotherapy than younger patients. (33-35). Therefore, in chapter 7 we studied the effect of age in palliative radiotherapy for painful bone metastases. At baseline, elderly patients (75 years and older) had a significantly lower performance score, as is to be expected since elderly patients represent a more fragile population than their younger counterparts. However, age did not independently predict for a pain response. Furthermore, the course of QoL after treatment was similar in elderly compared to younger patients for almost all domains, except for activity level impairment, which was higher in elderly, reflecting age specific limitations and not of the effect of radiotherapy. Thus, age does not have an effect on pain response or QoL after palliative radiotherapy. Therefore, there is no argument not to refer elderly patients for palliative radiotherapy, based only on age.

A limitation of our study could be referral bias, with only elderly patients in a good clinical condition being referred for radiotherapy. In our analyses, 20% of patients was 75 years or older, of which 39% was in a bad clinical condition, not being capable of taking care of themselves. So apparently, also elderly in a bad clinical condition were referred for treatment. Therefore, we believe this study is representative enough to conclude that age cannot be the reason not to refer patients for palliative radiotherapy.

Psychological distress

Psychological distress (PD) in patients with cancer is defined as a multi-factorial unpleasant emotional experience that may interfere with the ability of patients to cope effectively with their disease, its physical symptoms and treatment. (36) Psychological distress has a negative impact on QoL. (37) The Dutch guideline for psychosocial support in cancer patients aims to identify patients with high levels of distress who may be in need of an intervention, by using a screening instrument, the so-called "Lastmeter". The guideline states that early identification can prevent severe problems and have a positive impact on quality of life. (38) In chapter 4, we studied psychological distress before and after palliative radiotherapy, in order to be able to identify patients with a high level of psychological distress and offer them appropriate interventions. At baseline, 27% of patients had a high level of psychological distress. We found no relation between psychological distress at baseline and pain response. Only 15% of the variance in PD at baseline was explained by gender, age, performance status, pain score and self-reported QoL. However, we were not informed about some factors that might influence PD, like marital status, socio-economi-

cal status, level of education et cetera. The level of distress at baseline determined the level of distress after treatment, implying that physicians can identify high risk patients by screening at the referral for radiotherapy. However, having a high level of distress does not immediately imply a patients'need for referral for psychosocial support. (39) For radiotherapy departments, a specialized nurse might be useful, to screen for distress, speak with the patients and select those patients needing an intervention and willing to be referred.

Education

Education about (indications for) palliative radiotherapy and its effect on QoL should be incorporated in the training program of residents in any field of oncology. Studies among general practitioners show that the more knowledge they have of palliative radiotherapy, the higher the referral rate. (40,41) In Australia for example, only 78-80% of general practitioners would refer their patients with painful bone metastases and a prognosis of at least four months for palliative radiotherapy. (42) In the Netherlands, most general practitioners were aware of the effectiveness of radiotherapy for painful bone metastases. Nevertheless, only 47% ever referred patients for palliative radiotherapy, while 56% knew about possible side-effects. The most important reasons for not referring patients, were general condition, presumed discomfort of treatment and wish of the patient. (43) Hopefully our data will help other physicians determine whether their individual patient might benefit from palliative radiotherapy, inform them on the expected outcome and, when appropriate, refer those patients.

Past and current developments in radiotherapy for painful bone metastases

We studied the course of side-effects after treatment for painful spinal metastases in chapter 3, comparing two simple conventional treatment techniques, namely a single posterior-anterior (PA) field and two parallel opposed fields from anterior and posterior (APPA). The analyses demonstrated that radiotherapy technique is not an independent prognostic factor for abdominal or skin toxicity after treatment. However, after the DBMS, several developments took place.

Developments after the DBMS

Diagnostic imaging with computed tomography (CT) scans or MRI scans is nowadays standard of care. Simulation protocols, with the widespread use of computed tomography scans, have evolved over time. This gives opportunity to depict the actual radiation dose on the scans, making it possible to visualize the actual dose to target tissue and surrounding organs at risk. Furthermore, in the era of conventional radiography, margins were in

general set one vertebra above and below the metastasis. Since imaging and positioning verification have also improved over the years, margins for treatment can theoretically be reduced. (44) With current imaging techniques the metastasis and its clinical target volume can be delineated, following the guidelines of the International Spine Radiosurgery Consortium (45). However, patients often indicate a painful region or the majority of the spine is affected. Therefore it is debatable whether smaller field sizes will provide equal pain response rates as in the era of the DBMS.

Although conventional techniques are still frequently used to treat painful vertebral metastases, more advanced techniques, such as intensity modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT), become standard of care. These techniques facilitate a more conformal dose delivery and non-target tissues can be spared, in line with the ALARA-principle ("as low as reasonably achievable"). (46) Unfortunately, no studies are published comparing simple techniques with more conformal techniques, in terms of pain control, cost-effectiveness, QoL and patient satisfaction. When pain control, QoL and patient satisfaction are equal, these more conformal techniques are a better treatment option, although being more expensive and time consuming than the simple techniques. The advantages of more conformal dose distributions and sparing of organs at risk outweigh those disadvantages.

Nevertheless, little is known about the effect of the reduction in margins and smaller field sizes. This development should therefore be carefully monitored, data on pain response and retreatment rates should be gathered. Using cohorts of patients is a method becoming increasingly popular. An example is the OPTIMAL cohort, which is a prospective multicenter cohort collecting data on quality of life and pain in patients after radiotherapy and/or surgery of metastases of the long bones (see clinicaltrials.gov).

Another example is the PRESENT cohort (47) which is currently recruiting patients with painful bone metastases treated at a department of radiotherapy of a university hospital. This cohort collects information about baseline characteristics, pain, response to treatment, quality of life et cetera. In the future, cohorts like these will answer a variety of remaining questions in this patient group. They will probably also answer the question whether treatment of smaller fields results in comparable pain response rates as with conventional techniques.

In the appendix, we describe the study protocol of a randomized trial looking at preventing a temporary increase in pain, the so-called pain flare, after palliative radiotherapy. We studied two dose schedules of dexamethasone and placebo. (48) Inclusion was completed in March 2016, but was much slower than expected, since many patients met exclusion criteria, like the use of opioids, treatment of multiple sites or optimization of pain medication before treatment. Furthermore, the low inclusion rate was partially due to competing trials and the upcoming use of stereotactic radiotherapy. Slow inclusion rates seem to be a problem in studies in palliative patients. Therefore, the upcoming use of cohorts might boost the research in palliative care. The Canadian trial, comparing 8 milligrams of dexamethasone

with placebo, was already published. They showed a reduction in pain flare after treatment with dexamethasone in 298 patients treated with palliative radiotherapy. The incidence of a pain flare was 26% after dexamethasone and 35% with placebo. (49) Our database is currently updated and analysed, the results of our trial are expected soon.

Ongoing developments

Currently, other treatment techniques are emerging.

- *Stereotactic radiotherapy*

Stereotactic radiotherapy is an emerging treatment option for patients with painful bone metastases. Because of the steep dose gradient, the dose to the surrounding organs at risk, like the spinal cord, can be limited, while the dose at the target lesion can be intensified. (50,51) Single doses up to 16-24 Gy have been reported, with high radiologic tumor control rates of over 85%, without data on the pain response, since mainly local control was studied and the international definition of a pain response was not followed. (52,53) Toxicity rates, like radiation-related fractures or radiation-induced spinal cord toxicity, appear to be low. (53-56)

- *Protons*

Protons have a theoretical benefit over photons, due to the Bragg peak with rapid falloff of dose directly distally from the target, a sharp lateral penumbra and a low dose proximally from the target, thereby allowing also high and conformal dose depositions. Due to its characteristics, protons have potential benefits for patients, intensifying the dose to the target volume and lowering the dose to organs at risk. (57,58) So far, few patients with bone metastases have been treated with protons.

- *MR linear accelerator*

A recent development is a linear accelerator (linac) combined with a magnetic resonance imaging (MRI) scanner, the so-called MR-linac. The MRI provides optimal soft-tissue contrast and can therefore allow very accurate image-guidance during treatment. A possible benefit in patients with painful bone metastases might be dose escalation, mostly due to a better visualization of organs at risk, like the spinal cord. (59) Currently, few patients have been treated with the MR-linac for bone metastases.

Indications

The abovementioned techniques may have benefits in certain situations:

- *Dose*

A higher local dose might theoretically lead to a longer or better local control of the lesion. However, in a systematic review on treatment schedules in painful bone metastases, including schedules with 20 fractions of 2 Gy and 10 fractions of 3 Gy, a higher total dose did not lead to significantly higher pain response rates, neither in the group as a whole nor in subgroups (figure 1). (10,11) There seems to be a threshold below which treatment is less effective in terms of a pain response. This was shown in a randomized trial comparing a

single fraction of 4 Gy, 6 Gy and 8 Gy in patients with painful bone metastases. Patients treated with 6 or 8 Gy had a significantly higher pain response rate (73% and 78% respectively) than patients treated with a single fraction of 4 Gy (59%). The difference in pain response between a single fraction of 6 or 8 Gy was not significant. There was no difference in duration of a pain response or the rate of retreatment between those three doses. (60) A more recent trial compared a single fraction of 4 Gy with a single fraction of 8 Gy, in 651 patients with painful bone metastases. This trial showed a pain response after four weeks of 68% versus 80% for 4 and 8 Gy respectively. (61) To our knowledge, only one randomized trial compared a single fraction of 10 Gy with multiple fractions, showing an equal pain response rate. Of the 129 patients treated with a single fraction, pain response rate was 83,7%, but the amount and possible changes of pain medication were not taken into account. (62) In a systematic review by Tree on stereotactic radiotherapy in patients with oligometastatic disease, local control rates around 80% were noted, no data on pain response were given. Unfortunately almost all data were from single institution series and none of the studies was a randomized trial. (63) Nevertheless, no data are known showing that a dose higher than 8 Gy provides better pain control. Therefore, the optimal dose of a single fraction for painful bone metastases seems to be somewhere between 6 and 8 Gy. So, in the future, trials on higher doses delivered with aforementioned techniques in patients with bone metastases should report on pain response and QoL, instead of just local control rates. Furthermore, randomized trials in patients with painful bone metastases comparing conventional radiotherapy and those new techniques are important to determine the added value of stereotactic radiotherapy, protons or the MR-linac.

- *Retreatment*

When complaints of painful bone metastases return after previous radiotherapy, retreatment should be considered. However, the tolerance of surrounding normal tissue, like the spinal cord in vertebral metastases, limits the dose that can still be given locally, particularly when the interval between treatments is relatively short. Due to the aforementioned steep dose gradient, the dose to organs at risk can be reduced in stereotactic radiotherapy or protons, enabling retreatment in the future, which is most relevant in patients with a longer life expectancy.

- *Oligometastatic disease*

Patients with oligometastases (in bone or elsewhere) represent a relatively new group of patients with a maximum of four to five metastases, mostly limited to one site (e.g. bone, liver or lung), representing a subset of patients with a longer survival time than patients with more metastases. The focus of treatment is not only maintaining or improving quality of life, but also control of disease, prevention of local recurrences, delaying progression and possibly even leading to cure. (63-65) Therefore, this may be a subset of patients that particularly benefits from more advanced radiotherapy techniques. However, the presumption that more intensive treatment in patients with oligometastatic disease leads to better survival, remains to be proven.

Disadvantages

The main disadvantage of stereotactic radiotherapy, protons or the MR linac is the time investment it takes to prepare and deliver a treatment plan. Due to the steep dose gradients, image guidance during treatment is needed. Furthermore, additional imaging modalities are frequently needed such as MRI and the treatment planning is more complex and technically demanding. (50,51) As a result of this complexity, a one stop treatment, with intake, preparations and treatment within a few hours and thus just one hospital visit for the patient, is not possible with those techniques. Moreover, the costs are significantly higher compared to conventional treatment techniques (57,66) and treatment time is in general prolonged, which causes more inconvenience for the patients. Finally, these techniques, especially protons and the MR linac, are not widely available.

Ongoing trials

To our knowledge, two trials comparing stereotactic radiotherapy with conventional radiotherapy for painful bone metastases are currently ongoing. The Dutch RACOST trial is including patients with painful spinal metastases, randomizing between a single fraction of 20 Gy stereotactic radiotherapy and a single fraction of 8 Gy conventional radiotherapy. The primary objective is to investigate whether stereotactic radiotherapy leads to improved pain reduction compared to conventional radiotherapy without an increase of treatment related side-effects. Secondary endpoints are duration of the pain response, time to pain response and/or pain progression, toxicity, quality of life and the risk of spinal fractures. (67) In the RTOG 0631 trial, patients with painful spinal metastases are randomized between a single fraction of 8 Gy conventional radiotherapy and a single fraction of 16-18 Gy stereotactic radiotherapy. The dose of the stereotactic treatment, 16 or 18 Gy, is left to the decision of the treating physician. (68) The primary endpoint is pain response, but unfortunately this is not defined according to the international standards (18), making comparison with other trials difficult. Secondary endpoints include time to response, duration of a response, toxicity of treatment and quality of life.

Conclusion

Altogether, those new techniques sound like promising treatment options for selected patients, but their value still remains to be proven. Selection of patients needs to be clarified, to determine which patients benefit from these new treatments. Until the results of randomized trials are known, treatment of uncomplicated painful bone metastases with stereotactic radiotherapy should be performed in studies and otherwise be reserved for specific cases.

For the other two techniques, clinical trials should be performed confirming the benefits (69) and first results of clinical use should be awaited (59). For the majority of patients, a single fraction of 8 Gy conventional radiotherapy is the appropriate treatment of choice.

New developments outside radiotherapy

Apart from radiotherapy, other treatment strategies for bone metastases have emerged the last two decades after publication of the results of the DBMS.

Bisphosphonates

Bisphosphonates prevent bone resorption by reducing the number and activity of osteoclasts and are used to reduce the frequency and severity of skeletal-related events, like fractures, spinal cord compression, need for radiotherapy and hypercalcemia. (70) A recent systematic review studied the analgesic effect in patients with painful bone metastases and concluded that the evidence does not support the use of bisphosphonates to reduce existing pain. (71)

In the RIB trial, a single fraction of 8 Gy with conventional radiotherapy was compared with a single infusion of a bisphosphonate, ibandronate, in 470 prostate cancer patients with painful bone metastases. Overall, there was no difference in pain response after twelve weeks: 56,7% of patients treated with ibandronate versus 60,2% of patients treated with radiotherapy. However, pain response was more rapid after palliative radiotherapy, with a significant difference in response rates after four weeks, disappearing at the following time points. Toxicity, spinal cord compression, fractures, quality of life and survival were not different between treatment groups. (72) As a result of this trial, the golden standard remains a single fraction of 8 Gy, but when radiotherapy is not available or no option due to previous treatments, ibandronate seems a reasonable alternative. In the future, it would be interesting to study whether the combination of bisphosphonates and radiotherapy might further improve pain response rates and/or duration.

Radiopharmaceuticals

Radionuclides are administered intravenously and accumulate in sites of increased bone turnover. Subsequently, radiation is delivered at the osteoblastic metastatic sites, with the possible side-effect of bone marrow suppression. In a systematic review in patients with castrate-resistant metastatic prostate cancer, 36 articles were identified studying the effect of radiopharmaceuticals in patients with painful bone metastases, but an overall pain response could not be determined since different definitions of a pain response were used. In general, pain decreased in 50-60% of patients, while toxicity was mainly hematological. (73) For patients with metastatic breast cancer, limited evidence supports an effect of treatment. No well-designed trials showed superiority of radio-isotopes versus placebo and no trials showed non-inferiority or superiority of radio-isotopes versus radiotherapy or opioids in those patients. (74) The Cochrane review published in 2011, studied 15 randomized controlled trials in patients with metastatic bone pain and showed isotopes were effective in terms of pain relief. International criteria were not followed, any decrease in pain score was considered a pain response. Furthermore, only three of the trials were

considered to have low risk of bias. (75) The recently published ALSYMPCA trial randomized patients with bone metastases and no visceral metastases from castration-resistant prostate cancer between placebo and Radium-223. It showed a longer interval until the first symptomatic skeletal-related event and less use of external beam radio- therapy. Furthermore, an improvement in survival of three months was observed. Unfortunately, no data on pain scores were collected. (76) Currently, the α-RT trial is including patients, comparing Radium-223 combined with radiotherapy versus radiotherapy alone in patients with castration-resistant prostate cancer and painful bone metastases. The primary endpoint is the time to radiological progression, pain control is one of the secondary outcomes. The results of this trial will determine whether combining both treatments can be considered a treatment option for patients with metastasized prostate cancer and painful bone metastases. In conclusion, radionuclides are an effective treatment option, mainly in patients with multiple painful metastases. The major disadvantages are that only osteoblastic metastases respond to this treatment and the hematological toxicity.

Other local treatments

Surgical treatment, using internal fixation or intramedullary nailing of metastases in the long bones and/or pelvis, has been shown to provide pain relief, although the quality of the evidence is moderate. Treatment-related morbidity, like thrombosis or infection, is described in up to 21% of patients, depending on the type of procedure, with a perioperative mortality of up to 9% of patients. Furthermore, recovery time after surgery can be extensive, which can lead to a reduction of QoL. (77) Due to the high morbidity and mortality, this is mainly a treatment option in patients with (impending) fractures and a relatively long survival.

In local surgical procedures, like vertebroplasty or kyphoplasty, cement is inserted into the involved vertebra, using either an injection or a balloon respectively. The aim is to strengthen and restore the height of a collapsed vertebra. In a systematic review, 987 patients with bone metastases treated with vertebroplasty were studied. Pain reduction ranged between 47 and 87%. A pain response according to the international consensus could not be determined. Although the treatment is mostly performed using local anesthesia and considered safe, the review showed 5 deaths, attributable to the treatment, and 19 serious complications, mainly neuropathy. (78) In a recent publication, kyphoplasty in 31 patients with spinal metastases or multiple myeloma was studied. The authors noticed a pain reduction in all patients, but a pain response could not be determined. As a complication, on 13 treated levels, cement leakage appeared. (79) In conclusion, local surgical treatment seems a reasonable option in patients in whom the pain is caused by collapse of a vertebra due to bone metastases. Due to the limited evidence, in the Netherlands this treatment is not covered by insurance, which might play a role in decision making.

Radiofrequency ablation (RFA) is a minimally invasive treatment option, using thermal ablation which causes necrosis. Several small studies, with a maximum of 55 patients,

were published showing a decrease in pain after this treatment in patients with painful bone metastases. (80-82) In one of these studies, RFA was combined with cement augmentation, which appeared to be safe and effective in terms of decrease in pain score. (80) Disadvantages of RFA are the limitation of size of the metastasis and the need for sedation. Since the effect of RFA depends on distance to the tip of the electrode, RFA is often less efficacious at the border of the lesion..An interesting feasibility study compared radiotherapy with RFA followed by radiotherapy, in 45 patients with painful osteolytic bone metastases. This trial used the international criteria for response and documented an overall response rate of 93.3 % for the combined treatment, compared with 59.9% for radiotherapy alone (p:0.048). (83) Altogether, this sounds like a promising treatment option in selected patients in a good clinical condition, but results of larger trials have to be awaited.

High intensity focused ultrasound (HIFU), preferably with MRI guidance (MR HIFU), heats the target tissue. This leads to local elevation of the temperature and tissue destruction, indirectly ablating the periosteum and tumor tissue. (84) Several small single arm studies in patients with bone metastases were published. (85) The only randomized controlled single-blind trial showed a higher pain response after MR HIFU than placebo treatment. (86) No studies comparing MR HIFU with radiotherapy were published. Altogether, MR HIFU does not appear to be a replacement of palliative radiotherapy, due to the long treatment time, use of sedation, availability of the machine and the amount of patients that are ineligible for the treatment. (86,87)

Conclusion

In general, radiotherapy remains the golden standard for patients with painful bone metastases. In selected cases, for example patients who are ineligible for radiotherapy or have impending fractures or compression of the spinal cord, other treatment options, in particular surgery, may be considered. The value of other techniques remains to be proven in randomized trials.

Concluding remarks

This thesis focuses on several aspects on quality of life in patients with uncomplicated painful bone metastases, treated with palliative radiotherapy. The majority of patients will have a pain response after a single fraction of 8 Gy.
Since shared decision making and treatment individualization is important nowadays, it is insightful for both patients and physicians to be aware of the expected course of QoL in order to make individual treatment choices. Currently, it is not possible to predict which patients are not likely to benefit from treatment. Treatment of the great majority of patients with painful bone metastases is indicated, irrespective of factors like age and survival. The only group of patients in whom referral should be carefully considered, are those with a very low life expectancy, i.e. patients in a bad clinical condition. There are several new radiotherapy techniques, but their superiority over more conventional treatment techniques for irradiating painful bone metastases remains to be proven. It is likely that only a minority of patients with painful bone metastases will benefit from those new treatment strategies.
For future trials, it is of upmost importance to follow the guidelines from the international consensus, to be able to determine the pure effect of treatments on pain and to compare different treatment strategies.

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9

Appendix

Dexamethasone for the prevention of a pain flare after palliative radiotherapy for painful bone metastases: a multicenter double-blind placebo-controlled randomized trial

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Abstract

Background: Radiotherapy has a good effect in palliation of painful bone metastases, with a pain response rate of more than 60%. However, shortly after treatment, in approximately 40% of patients a temporary pain flare occurs, which is defined as a two-point increase of the worst pain score on an 11-point rating scale compared to baseline, without a decrease in analgesic intake, or a 25% increase in analgesic intake without a decrease in worst pain score, compared to baseline. A pain flare has a negative impact on daily functioning and mood of patients. It is thought to be caused by periostial edema after radiotherapy. Dexamethasone might diminish this edema and thereby reduce the incidence of pain flare. Two non-randomized studies suggest that dexamethasone reduces the incidence of a pain flare by 50%. The aim of this trial is to study the effectiveness of dexamethasone to prevent a pain flare after palliative radiotherapy for painful bone metastases and to determine the optimal dose schedule.

Methods and Design: This study is a three-armed, double-blind, placebo-controlled multicenter trial. We aim to include 411 patients with uncomplicated painful bone metastases from any type of primary solid tumor who receive short schedule radiotherapy (all conventional treatment schedules from one to six fractions). Arm 1 consists of daily placebo for four days, arm 2 starts with 8 mg dexamethasone before the (first) radiotherapy and three days placebo thereafter. Arm 3 consists of four days 8 mg dexamethasone. The primary endpoint is the occurrence of a pain flare. Secondary endpoints are pain, quality of life and side-effects of dexamethasone versus placebo. Patients complete a questionnaire (Brief Pain Inventory with two added questions about side-effects of medication, the EORTC QLQ-C15-PAL and QLQ-BM22 for quality of life) at baseline, daily for two weeks and lastly at four weeks.

Discussion: This study will show whether dexamethasone is effective in preventing a pain flare after palliative radiotherapy for painful bone metastases and, if so, to determine the optimal dose.

This study is registered at ClinicalTrials.gov: NCT01669499

Background

Radiotherapy, with a single fraction of 8 Gray as the gold standard, has a good effect in palliation of painful bone metastases, with a pain response rate of more than 60%. (1) However, a possible side-effect is a transient progression of pain, the so-called pain flare. This pain flare is defined as a two-point increase of the worst pain score on an 11-point rating scale, compared to baseline, without a decrease in analgesic intake, or a 25% increase in analgesic intake without a decrease in worst pain score. A pain flare is distinguished from progression of pain by requiring the worst pain score and analgesic intake to return to baseline levels after the flare. (2)

Two prospective observational studies show that approximately 40% of patients experience a pain flare. (3, 4) Hird studied 111 patients with uncomplicated painful bone metastases and showed an incidence of pain flare of 40%, with no difference between single or multiple fractions. The median duration of a pain flare was 1.5 days, while 25% of patients had more than one pain flare. Most of the pain flares occurred during the first five days after treatment. A pain flare occurred in 52% of patients with breast cancer and in 25% of patients with prostate cancer. (3) Loblaw studied 44 patients and found, with an adjusted, underestimating definition of a pain flare, an incidence of 41%, with a significant difference between single and multiple fractions (57% and 24% respectively). (4)

A survey among patients who experienced a pain flare showed that having a pain flare had a negative effect on daily functioning of patients and on their mood. (5) Most patients tried to manage their pain flare by increasing their pain medication, at the cost of possible side-effects. The majority of patients who experienced a pain flare stressed the need for prevention of this pain flare instead of managing it with breakthrough medication.

The pain flare is thought to arise through edema of the periostium of the irradiated bone. Dexamethasone, an anti-inflammatory drug decreasing edema, may be an effective drug. Two small studies were performed to study the effect of dexamethasone on the incidence of pain flare. (6, 7). In the study by Chow a single dose of 8 mg dexamethasone was prescribed one hour before the single fraction radiotherapy. This study included 33 patients and showed an overall pain flare incidence of 24%. Most of the observed pain flares commenced after the half-life of dexamethasone (7), suggesting that a longer treatment time might be useful. Dexamethasone was well tolerated. A subsequent study, with 41 evaluable patients, used 8 mg dexamethasone before single fraction radiotherapy and then daily for three consecutive days. It showed an overall incidence of pain flare of 22%, with a median duration of one day. (6)

Both studies concluded that randomized trials are necessary to study the effectiveness of dexamethasone for prevention of a pain flare. No randomized trials have been published so far. Therefore, the aim of this trial is to study the effectiveness of dexamethasone to prevent a pain flare after palliative radiotherapy for painful bone metastases and to determine the optimal dose schedule.

Methods / Design

Design

This three-armed, prospective, randomized, placebo-controlled multicenter study is being led by the University Medical Center Utrecht. The study is supported by grants from the Dutch Cancer Society and ZonMw. It is registered at ClinicalTrials.gov: NCT01669499. The study compares two different dose schedules of dexamethasone with a placebo (Figure 1). The aim is to study the effectiveness of dexamethasone to prevent the occurrence of a pain flare after radiotherapy for painful bone metastases and to define the optimal schedule of dosing. Secondary endpoints are pain scores, quality of life and side-effects of placebo and dexamethasone. In addition, the predictive value of a pain flare for response to the palliative radiotherapy will be studied.

Patients

The study includes patients with uncomplicated painful bone metastases from a solid tumor, who are referred for a short course of palliative radiotherapy. Short course radiotherapy encompasses all conventional treatment schedules from one to six fractions of radiotherapy. The full inclusion and exclusion criteria are listed in Table 1. Patients are randomized between the three treatment arms (Figure 1), after stratification for center and treatment schedule: single or multiple fractions. Randomization is performed by telephone at the Comprehensive Cancer Center The Netherlands. Double-blind randomization is guaranteed by only communicating the number of the medication box to patients and physicians.

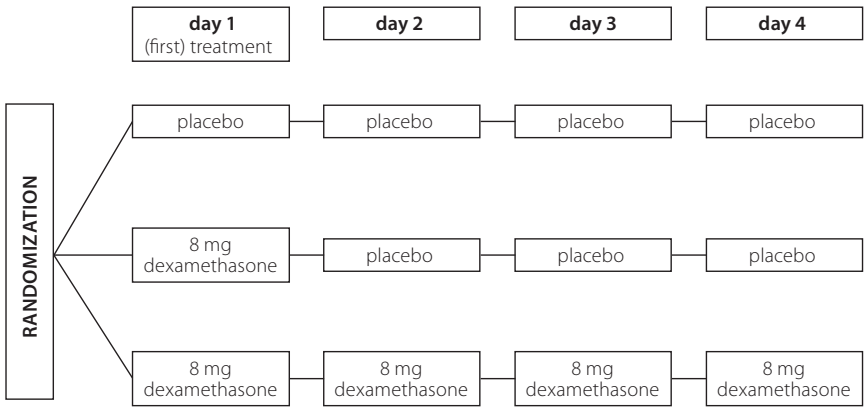

Figure 1 Treatment arms.

Table 1 Full inclusion and exclusion criteria.

Inclusion	Patients of 18 years or older
	Uncomplicated painful bone metastases
	Primary malignancy is a solid tumour
	Pain intensity on a numeric rating scale of 2-8
	No immediately expected change in the analgesic regimen.
	Indication for single or short course radiotherapy
	Able to fill out Dutch questionnaires
	Able to follow instructions
	Informed consent provided
Exclusion	Patients with haematological malignancy
	Multiple sites to be irradiated
	Patients who have been treated before with palliative radiotherapy
	for painful bone metastases to the same bony localisation
	Current use of steroids (dexamethasone, prednisolone or other), use up to less
	than a week before randomization or expected use within 2 weeks after
	start of radiotherapy (e.g., as part of anti-emetic regimen for chemotherapy)
	Contraindications for the use of dexamethasone (to be judged by the radiation-oncologist)
	Long-term schedule radiotherapy (>6 fractions)
	Life expectancy shorter than 8 weeks
	Karnofsky Performance Score of 40 or less

Participating centers

In total, 12 out of the 21 radiotherapy departments in the Netherlands participate in this nationwide study. Patients are asked for participation at these departments. Participating centers are:

University Medical Center Utrecht, Utrecht; Leiden University Medical Center, Leiden; MAASTRO Clinic, Maastricht; Medical Center Haaglanden, den Haag; The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam; Medical Spectrum Twente, Enschede; Erasmus Medical Center, Rotterdam; ARTI Institute for Radiation Oncology Arnhem, Arnhem; Institute Verbeeten, Tilburg; Catharina Hospital, Eindhoven; Zeeuws Radiotherapeutic Institute, Vlissingen; Reinier de Graaf Gasthuis, Delft

Ethics, informed consent and safety

The protocol has been approved by the medical ethics committee of the University Medical Center Utrecht. In the participating centers, local medical ethics committees have

approved the protocol. The study is conducted in accordance with the Declaration of Helsinki. Written informed consent, signed and dated, is obtained before randomization. Serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSAR), as defined in the study protocol, are reported to the central medical ethics committee and to the central committee of medical research involving human subjects.

Endpoints and analysis

Participating patients fill out a questionnaire at baseline (the start of treatment, defined as day 1), then daily until day 15 and a final questionnaire at day 29. The questionnaire contains the Brief Pain Inventory (8), which notes the level of pain on a 11 point pain scale ranging from 0 (no pain) to 10 (worst imaginable pain). Two questions are added about side-effects of the study medication ('Do you have appetite?' and 'Do you feel restless?'). To assess quality of life, the EORTC QLQ-C15-PAL (9) and the EORTC QLQ-BM22 (10) are added (both at baseline, day 8, 15 and 29). Reminder telephone calls are performed twice during the study. The researchers contact participants who do not return their questionnaires. The occurrence of a pain flare, the primary endpoint of the study, is determined using the daily noted pain scores and pain medication. Pain response and side-effects of placebo and dexamethasone are assessed by the daily questionnaires.

Analysis will be by intention-to-treat. Patients who have received at least one fraction of radiotherapy, irrespective of study medication intake, and have returned questionnaires are evaluable. Descriptive analyses of baseline characteristics will be performed. Comparison of occurrence of pain flare between the three arms will be assessed using the Chi-Square test. Comparison of pain intensity, quality of life items and side effects at baseline and over time between the three arms will be done using multilevel analysis. Since the risks of the study using well-known medication are considered minimal, an interim analysis will not be performed.

Power calculation

Assuming a reduction of 50% (from 40 to 20%) of the occurrence of a pain flare by administering a single dose of 8 mg dexamethasone, a total of 411 patients are necessary (137 per arm) to reach a power of 90% given a significance level of 5% (2-sided), and assuming a drop-out of 20% during follow-up. In the Netherlands, around 3000 patients are eligible for this study yearly. With 12 out of 21 institutions participating and an estimated participation rate of 20%, the total study time needed is about 2 years.

Discussion

Up to 40% of patients experience a pain flare after palliative radiotherapy for painful bone metastases.(3, 4) A pain flare severely impacts functional activity and mood of patients. (5) Therefore, it is clinically important to prevent the occurrence of a pain flare. Earlier publications suggest an effect of dexamethasone on the incidence of pain flare. (6, 7) Although side-effects of a short course and relative low dosage of dexamethasone are considered minimal, the beneficial effect in this patient population should be proven before integrating dexamethasone medication into daily clinical radiotherapy practice. A prolonged schedule of dexamethasone might be better in preventing a pain flare. Therefore, in the present trial, we study different schedules, to be able to determine which one is the optimum schedule.

A recent publication from Chiang et al. (published after the initiation of our study) in patients treated with stereotactic radiotherapy for painful bone metastases showed an incidence of pain flare of 68%. However, this might be an overestimation. Firstly, they did not mention to require pain score and analgesic intake to return to baseline, to distinguish it from progression. Secondly, initiation of corticosteroids during or after treatment was considered to be indicative of a pain flare (11) Nevertheless, these results give rise to the assumption that this group of patients might also benefit from our treatment results. However, the results of our study are not directly applicable to patients who are treated with stereotactic radiotherapy for painful bone metastases, since they represent a highly selected group of patients who receive much higher total doses of radiotherapy (e.g. 1x 20 Gy, or 3x 8 Gy).

Using consensus definitions of endpoints in literature is important, to be able to compare studies.(12) Most published studies concerning pain flare after palliative radiotherapy use the definition by Chow (2), incorporating pain scores, analgesics intake and returning to baseline to distinguish it from progression. Loblaw et al.(4) used a different definition for pain flare. They tried to convert it into the definition by Chow (2), but since they used a different pain scale, this was not completely possible, which made it difficult to interpret and compare these results with other published studies. We chose to also use the definition by Chow (2), to enable comparison with other studies.

In conclusion, if this study proves the effectiveness of dexamethasone in the prevention of a pain flare after palliative radiotherapy for painful bone metastases, this should lead to a change in supportive care. Since we use a commonly accepted definition of pain flare, comparison between our results and future results from other trials may be possible. It may also lead to studies of the benefit of dexamethasone in preventing a pain flare after stereotactic radiotherapy.

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10

Summary

Summary in Dutch (Nederlandse samenvatting)

Publications

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Dankwoord

Summary

Introduction (chapter 1)

In the majority of patients with metastasized cancer, the focus of treatment is no longer cure, but other treatment goals, such as local control, relieving symptoms, prolonging life and maintaining or improving quality of life (QoL). Bone metastases are common in those patients and may lead to pain, fractures, neurologic deficits and/or hypercalcemia. Pain is reported in over 70% of patients with bone metastases and has a negative impact on QoL. Pain control is therefore very important. Pharmacological treatment is the first treatment option, although this may not reduce the pain sufficiently or cause too many side effects. Another important treatment option is palliative radiotherapy, used in almost 75% of patients with bone metastases. The largest randomized trial worldwide is the Dutch Bone Metastasis Study (DBMS), which studied pain response after a single fraction of 8 Gray (Gy) versus six fractions of 4 Gy in 1157 patients with uncomplicated painful bone metastases. The study was first published in 1999 and showed equal effectiveness, with a pain response rate of 71%. After publication of international standards in clinical trials on bone metastases in 2002 (redefining a pain response), a re-analysis was performed in 2003, taking into account changes in pain medication. This analysis showed a pain response of 71% and 73% for the single and multiple fractions respectively. The equal effectiveness of a single fraction compared to multiple fractions was confirmed in several systematic reviews and no differences in toxicity were observed. Furthermore, the DBMS has shown that a single fraction is also preferred in terms of cost utility benefits. A prognostic model was developed for patients with painful vertebral metastases, to be able to determine for which patients invasive treatments like surgery are indicated. For patients with femoral metastases, the amount of axial cortical involvement turned out to be predictive for the chance of developing a fracture, leading to a better selection of patients in whom prophylactic surgery may be indicated. Other analyses showed that a single fraction is also preferred for patients with a long survival. For patients who did not achieve a pain response after radiotherapy or who experienced progression after an initial response, retreatment can be considered. A recent randomized trial in retreated patients, studying a single fraction of 8 Gy versus 20 Gy in multiple fractions, reported a pain response of around 45-50% in both groups. In conclusion, in the majority of patients with uncomplicated painful bone metastases, a single fraction of 8 Gy is the golden standard for both primary treatment and for retreatment. Despite this overwhelming evidence, research shows that in daily clinical practice, patients are still treated with a variety of treatment schedules, or no treatment at all. The goal of this thesis is to increase insight in palliative radiotherapy for painful bone metastases. Furthermore, we aimed to help physicians determine the most optimal treatment strategy for their individual patient.

Predicting survival

In chapter 2 we describe the development of a prognostic model for patients with painful bone metastases. Estimating prognosis is important for both patients and their caregivers, for example to make treatment decisions and weigh the time investment and toxicity of a treatment against the expected benefit and the duration of and to this effect. Several prognostic models exist, but these are infrequently used in daily clinical practice, mainly due to complexity or use of variables that are not commonly available. Our goal was to develop a simple prognostic tool to aid patients and physicians in decision making. We used the data of the DBMS and, for external validation, a more recent cohort of 934 patients treated with radiotherapy for painful vertebral metastases between 2001 and 2010. The mean age in the DBMS was 65 years. Most patients had breast (39%), prostate (23%) and lung cancer (25%). The mean Karnofsky performance status was 70. Median and mean survival were 30 and 49 weeks respectively. Univariate analysis showed that being male, being older than 65 years, having any primary tumor other than breast cancer, having visceral metastases, lower performance score, lower score for general health, worse valuation of life and higher pain score were associated with a higher risk of death. In multivariate analysis, the best predictive model included gender, primary tumor, presence of absence of visceral metastases, performance score and scores for general health and valuation of life, with a C-statistic of 0.72. This is considered a reasonable discriminative ability. Since the aim was to develop a simple tool, we simplified the model to two widely available variables, namely performance status and primary tumor. This model had a comparable discriminative ability (C-statistic of 0.71). The calibration plot indicated that the model was overly pessimistic and predicted best in patients with a poor prognosis, namely patients with other primary tumors than breast or prostate cancer and a bad performance score. This is the patient group in whom physicians are particularly interested to determine whether they will live long enough to benefit from treatment. In the external dataset, 934 patients were included, with a mean age of 65 years, having mainly breast (29%), prostate (21%) or lung cancer (25%). The mean performance status was 70. Median and mean survival were 21 and 60 weeks respectively. The simple model with only primary tumor and performance status, showed a C-statistic of 0.72 and an almost identical calibration plot. The final model, including primary tumor and Karnofsky performance status, shows a reasonable discriminative ability. The survival table, based on those two variables, provides insight for physicians enabling them to make treatment decisions together with their patients, based (among other factors) on an adequate estimation of survival.

Toxicity

Side-effects from radiotherapy on painful bone metastases are in general mild. Rates of side-effects of around 50% are reported, consisting mainly of nausea and/or vomiting. The side-effects depend largely on location of the radiation field. In patients with painful vertebral metastases, two conventional treatment techniques are frequently used, namely a single posterior-anterior (PA) field and two opposing anterior-posterior and posterior-anterior (APPA) fields. In chapter 3 we describe the toxicity of both treatment techniques. Data of 343 patients treated for vertebral metastases within the DBMS were used. Patients filled out thirteen weekly extensive questionnaires on pain, medication, physical complaints and quality of life, followed by monthly questionnaires afterwards, until two years of follow-up, death or closure of the study. Of the 343 studied patients, 250 were treated with a PA field, 93 patients (27%) with an APPA technique. Treated locations were the lumbar spine (53%), the thoracic spine (34%) or overlapping locations (13%). Treatment technique depended on treatment institute and not on individual patient characteristics. Baseline characteristics did not differ between treatment groups, with one exception: patients treated with a PA field more frequently received systemic therapy than those treated with an APPA technique (59% versus 43%). The pain response rate was 74% and comparable between both groups. In general, side-effects were minor. Patients treated with APPA fields showed slightly more abdominal complaints than those treated with a PA field, namely significantly more diarrhea, with a trend for more vomiting and abdominal pain. In multivariate analysis, treatment schedule and location were predictive for abdominal complaints. For skin complaints, primary tumor and location were predictive. Treatment technique did not predict for skin or abdominal complaints after treatment. Although more conformal treatment techniques are available nowadays, the benefits of these new techniques have not yet been proven. Furthermore, these new techniques are, in general, more time consuming in terms of treatment planning and delivery and more expensive. Therefore, conventional techniques using a single fraction of 8 Gy will continue to be used, without a preference for a PA or APPA field.

Psychological distress

Psychological distress (PD) has a major impact on patients and is associated with symptoms like nervousness, worrying, anxiety and depression. Those symptoms are experienced by almost 50% of incurable cancer patients. Although several interventions exist, like psychosocial interventions, cognitive therapy or psycho-educational interventions, only a minority of patients is referred. This may partly be due to under-identification of those patients with a high level of PD. In chapter 4, we studied the incidence and course of PD in patients treated with radiotherapy for painful bone metastases in the DBMS. The Rotterdam

Symptom Checklist from the questionnaires was used, which consists of a subscale for PD, including irritability, worrying, depressed mood, nervousness, despairing about the future, tension and anxiety, and ranges from 7 (no PD) to 28 (maximum amount of PD). The mean level of PD at baseline was 13.4, with a median of 12.0. Twenty-seven percent of patients had a high level of PD at baseline (≥17). Patients with high PD were mainly female, had breast cancer, had a low Karnofsky performance status and low scores for QoL. The multivariate analysis showed that age, gender, Karnofsky performance status, pain score and scores for QoL were predictive for PD. Female patients, higher age, worse performance status, lower pain score and worse self-reported QoL were associated with an increased chance of high levels of PD. The area under the curve was 0.71, indicating moderate discriminative ability. When studying the course of PD, the mean score for the entire group remained constant over time. For those patients with a high level of PD at baseline, the mean level of PD decreased the first weeks after treatment and stabilized around the threshold value. When studying only those patients still returning questionnaires after three months, representing patients in a better clinical condition, the course of PD remained similar, although with slightly better scores. In conclusion, over 25% of patients experiences PD before treatment and stays around the threshold level after treatment. Screening might be helpful to identify those patients most in need for interventions, in order to improve or maintain QoL.

Quality of life

Health-related QoL is a multidimensional construct, taking into account both positive and negative aspects of physical, emotional, cognitive and social functioning, in relation to the sequelae of a disease and its treatment. Although QoL of patients is an important endpoint in palliative care, few of the randomized trials in palliative radiotherapy for painful bone metastases, document the impact of bone metastases and its treatment on QoL. The studies that reported about QoL have limitations, like a short follow-up or only studying general QoL instead of the separate domains. In chapter 5 we studied and modeled the detailed course of different domains of QoL after radiotherapy for painful bone metastases, using the data of the DBMS. Furthermore, we analyzed the influence of several baseline and follow-up variables on the course of QoL. All QoL items in the QoL questionnaire (mainly consisting of the RSCL) were studied, using principal component analysis to define clinically meaningful and relevant sum scores. We identified three domains, namely physical health, psychosocial health and functional status. We found that the level of QoL was related to the actual survival. After treatment with radiotherapy, in the first week a deterioration occurred for the physical and functional domain and in perceived general health, which stabilized afterwards for the latter two and which improved for the physical domain. Only in the psychosocial domain, an improvement of QoL was noticed after

treatment. Afterwards, the course of QoL remained quite stabile for most of remaining life span, with a steep deterioration of QoL several weeks before the end of life. This pattern was noticed for all QoL domains. Higher baseline pain score and intake of opioids were associated with lower levels of QoL for almost all domains, with varying effect sizes. A lower baseline performance status and a higher age were associated with a worse functional QoL. Compared to patients with other types of primary tumor, patients with prostate cancer had a lower physical and functional QoL, while patients with breast cancer had a lower functional QoL, although this effect was small. Radiotherapy schedule was not related to QoL, except for the physical domain: patients treated with six fractions of 4 Gy showed a temporary worsening of physical QoL during the first weeks after treatment, compared to patients treated with a single fraction of 8 Gy. Thus, in general, QoL stabilized after palliative radiotherapy for painful bone metastases. Stabilization might be the effect of treatment, since without treatment deterioration could be expected in most patients. Although the majority of patients experienced a pain response, QoL did not clearly improve after treatment, which is possibly due to the multidimensional concept of QoL, not only involving physical complaints like pain, but also psychosocial and functional problems. Furthermore, in metastasized cancer, QoL is influenced by many other physical symptoms, due to the disease and/or its treatment. Nevertheless, in a population like this, stabilization of QoL is an important and meaningful outcome. In chapter 6 we studied QoL in relation to a pain response, since one might expect a better QoL in patients with a pain response compared to patients who did not experience a pain response. Our secondary goal was to identify factors predictive for a pain response after radiotherapy for painful bone metastases, to determine who should and who should not be offered palliative radiotherapy. So far, it is unsure to what extent a response to radiotherapy leads to an improvement of QoL. We used the data of all 956 patients with breast, prostate and lung cancer within the DBMS, in whom a pain response could be determined. We excluded patients with other primary tumors, since this group was considered too heterogeneous. Studied QoL domains were psychological distress, physical symptom distress, activity level impairment, perceived general health and a score for general valuation of life. In total, 722 (76%) of 956 patients experienced a pain response after radiotherapy, with a median time to response of three weeks. At baseline, non-responders had significantly more activity level impairment and a worse perceived general health compared to responding patients. Other QoL subscales did not differ at baseline. In the twelve weeks after radiotherapy, non-responding patients showed a worse QoL for all domains compared to responding patients. Most QoL domains improve in responding patients and deteriorate in non-responding patients. Only activity level impairment remained stable in responding patients, but deteriorates in non-responding patients. The differences between both groups were small during the first weeks after treatment, but increased over time, becoming clinically relevant. At baseline, non-responding patients were more likely to have lung cancer, visceral metastases and a worse physical condition

and less likely to receive systemic therapy prior to radiotherapy. Responding patients had a significantly better survival than non-responding patients, with a median survival of 16 weeks compared to 45 weeks for responding patients. The final model predicting a pain response after palliative radiotherapy included primary tumor, age, performance status, presence of visceral metastases and use of opioids. Breast or prostate cancer, younger age, good performance status, no visceral metastases and use of opioids were associated with a higher chance of responding to treatment. However, the discriminative ability of the model was very low (C-statistic of 0.55), making it useless for daily clinical practice. Analyzing by tumor type, in patients with breast cancer, younger age and no visceral metastases were associated with a higher chance of pain response after radiotherapy. For patients with prostate or lung cancer, no additional predictors were identified. In conclusion, patients responding to radiotherapy for painful bone metastases show a better QoL afterwards than patients without a pain response. Patients with poor QoL at baseline are less likely to have a pain response. We were unable to develop a model to accurately predict which patients are most likely to achieve a pain response.

Effect of age

The number of elderly cancer patients increases, due to several factors, like a longer life expectancy, ageing of the baby boom era and improved cancer treatments. Elderly cancer patients represent a different population than younger patients, in general they are more fragile, with age-specific needs, related to multimorbidity and poorer physical and/or cognitive condition. Since elderly are frequently excluded from trials, trial outcomes may not be applicable to this group of patients. It has been shown that elderly cancer patients are frequently treated differently from younger patients, e.g. receiving less often palliative radiotherapy. In chapter 7 we studied the effect on age on a pain response after palliative radiotherapy for painful bone metastases, in order to determine whether this treatment is justified in elderly patients. In total, in the DBMS, 20% of patients was 75 years and older, 35% was between 65 and 74 years and 45% below 65 years. Elderly patients (≥ 75 years) were more likely to be male and to have prostate cancer. More elderly patients were not able to take care of themselves: 39% versus 26% of patients younger than 65 years. The overall pain response did not significantly differ between age cohorts: 67% of elderly patients had a pain response, compared to 74% of patients between 65 and 74 years and 78% of patients below 65 years. Age was not an independent predictor for pain response. All QoL subscales were comparable between age cohorts both at baseline and during follow-up, except for activity level impairment. At baseline, elderly patients had more activity level impairment than younger patients, this difference remained significant during follow-up. In conclusion, age was not a predictor for pain response or QoL after palliative radiotherapy for painful bone metastases. Both at baseline and after radiotherapy,

elderly patients did not evaluate their overall QoL inferior compared to younger patients. Therefore, higher age should not be a reason to withhold palliative radiotherapy.

Discussion and future perspectives

In chapter 8 the contribution of the DBMS to knowledge and treatment recommendations in radiotherapy in patients with painful bone metastases is described. Synchronizing methodology in trials in patients with painful bone metastases is highly recommended, to be able to compare the results of different trials and different treatment strategies. Using similar treatment outcomes and similar definitions of a pain response, including the use of pain medication, is important. Prognostic models, which are increasingly used in daily clinical practice, should be developed in accordance with methodological guidelines and its critical application should be covered in the education of cancer specialists and other physicians. Furthermore, new developments in radiotherapy for painful bone metastases are discussed, in particular stereotactic radiotherapy, protons and the MR linac. These options are more expensive and time consuming and their added value in treating patients with painful bone metastases remains to be proven. With regard to dose, no data are available showing that a higher total dose results in higher pain response rates or a longer duration of pain response. For stereotactic radiotherapy two trials are currently ongoing, randomizing between a single fraction of 8 Gy and stereotactic treatment in patients with spinal metastases. The outcomes of these trials will be very important to determine the place of stereotactic radiotherapy in the treatment of patients with painful bone metastases. For the use of protons and the MR linac, clinical trials should be undertaken proving their added value before treating patients with those techniques.
New developments outside radiotherapy include the use of bisphosphonates, which are frequently prescribed to reduce the frequency of skeletal-related events. In a randomized trial, over 56% of patients using ibandronate show a pain response, making it an alternative treatment when radiotherapy is not an option. Radionuclides show a pain response in 50-60% of patients, but has not been proven to be equal or better than radiotherapy for localized pain. They are mainly a treatment option in patients with pain at multiple sites and osteoblastic bone metastases. Surgical treatment may be considered in patients with (impending) fractures and a relatively long survival. Due to a high complication rate and mortality, local surgical procedures, like vertebroplasty or kyphoplasty, seem no treatment option, even more since no data on pain response are known. For relatively new procedures, like radiofrequency ablation (RFA) and magnetic resonance high intensity focused ultrasound (MR HIFU), randomized trials should be awaited. Due to the complexity and circumstances of treatment, those treatments are not expected to become a regular treatment option. In conclusion, although developments in and outside radiotherapy have occurred over the years, a single fraction of 8 Gy palliative radiotherapy remains the

golden standard in the vast majority of patients with painful bone metastases. In selected cases, like (impending) fractures or spinal cord compression in patients in a good clinical condition and relatively long survival, surgery may be indicated.

Pain flare

The appendix contains the study protocol of a recent trial in patients treated with radiotherapy for uncomplicated painful bone metastases. A temporary increase in pain after radiotherapy, the so-called pain flare, occurs in approximately 40% of patients. A pain flare is defined as a two-point increase of the worst pain score on an 11-point rating scale compared to baseline, without a decrease in analgesic intake, or a 25% increase in analgesic intake without a decrease in worst pain score, compared to baseline. It has a negative impact on QoL and is thought to be caused by periostial edema. Dexamethasone might diminish this edema and may therefore be effective in reducing the incidence of a pain flare. Two non-randomized studies already suggest that dexamethasone reduces the incidence of a pain flare by 20%. Recently, a randomized trial reported a decrease of pain flare with dexamethasone compared to placebo, 26% versus 35% respectively (p:0.05). This trial compared one dose schedule of dexamethasone with a placebo. Our randomized double-blind multicenter trial has three arms: two dosage schedules of dexamethasone and one arm with placebo. The primary endpoint is the occurrence of a pain flare, secondary endpoints are pain, QoL and side-effects of medication. The study has included the needed 294 patients in March 2016. Results are expected soon.

Summary in Dutch | Nederlandse samenvatting

Introductie (hoofdstuk 1)

Bij de meeste patiënten met uitgezaaide kanker is genezing niet langer het doel van behandeling, maar worden andere doelen nagestreefd, zoals locale controle, symptoombestrijding, levensverlenging en behoud of verbetering van kwaliteit van leven (KvL). Uitzaaiingen in het bot (botmetastasen) komen veel voor bij patiënten met uitgezaaide ziekte en kunnen leiden tot pijn, botbreuken, neurologische problemen en/of een verhoogd calciumgehalte in het bloed. Pijn wordt door 70% van de patiënten met botmetastasen aangegeven en heeft een negatief effect op hun KvL. Het is dus erg belangrijk om deze pijnklachten onder controle te krijgen. Pijnmedicatie is vaak de eerste stap in de behandeling, dit is echter niet altijd voldoende effectief of geeft veel bijwerkingen. Een andere belangrijke mogelijkheid voor behandeling is palliatieve bestraling). Ongeveer 75% van de patiënten met pijnlijke botmetastasen wordt bestraald.
De Nederlandse botmetastasen studie (Dutch Bone Metastasis Study, DBMS) is de grootste gerandomiseerde studie wereldwijd naar bestraling in patiënten met ongecompliceerde pijnlijke botmetastasen. In deze studie werd een eenmalige bestraling met een dosis van 8 Gray (Gy) vergeleken met zes bestralingen van 4 Gy. De uitkomsten werden gepubliceerd in 1999 en toonden gelijke effectiviteit van beide schema's, waarbij 71% van de patiënten reageerde met een pijnrespons (afname of verdwijnen van de pijn). Na deze publicatie verscheen een internationale consensus, waarin eindpunten werden beschreven in studies naar bestraling bij patiënten met pijnlijke botmetastasen. In deze consensus werd een pijnrespons gedefinieerd, waarin ook het gebruik van pijnmedicatie werd meegenomen. Hierop werd een nieuwe analyse verricht, waarbij de pijnrespons 71% en 73% bedroeg, bij respectievelijk één en zes bestralingen. Dat één bestraling net zo effectief is als meerdere bestralingen, werd bevestigd in meerdere overzichtsartikelen, waarbij geen verschillen in bijwerkingen werden waargenomen. De DBMS heeft aangetoond dat ook met betrekking tot kosteneffectiviteit een eenmalige bestraling de voorkeur heeft.
Een model werd ontwikkeld om de overleving te voorspellen van patiënten met pijnlijke wervelmetastasen, aangezien een betrouwbare inschatting van de levensverwachting belangrijk is voor het vaststellen van de indicatie voor chirurgische behandeling. Voor patiënten met een uitzaaiing in het bovenbeen werd gevonden dat de lengte van de uitzaaiing voorspellend is voor het risico op een botbreuk. Hierdoor kunnen patiënten worden geselecteerd waarvoor een operatie geïndiceerd is om een botbreuk te voorkomen. Verder is aangetoond dat een eenmalige bestraling ook de voorkeur heeft bij patiënten met een relatief lange overleving.
Herbestraling kan worden overwogen bij patiënten die niet hebben gereageerd op de eerste bestraling of die opnieuw pijn krijgen na een eerdere respons. Een recente ge-

randomiseerde studie onderzocht voor herbestraling een eenmalige bestraling van 8 Gy en 20 Gy in meerdere bestralingen. Deze studie toonde dat 45-50% van de patiënten met beide behandelschema's een pijnrespons ontwikkelde. Concluderend is een eenmalige bestraling van 8 Gy de gouden standaard voor patiënten met pijnlijke botmetastasen, zowel bij de eerste behandeling als bij herbestraling.
Ondanks dit overtuigende bewijs wordt in de dagelijkse praktijk nog steeds met diverse bestralingsschema's behandeld, en zijn er patiënten bij wie van bestraling wordt afgezien. Het doel van dit proefschrift is om het inzicht te vergroten in palliatieve bestraling bij patiënten met pijnlijke botmetastasen. Verder is het doel om artsen te ondersteunen in het bepalen van de optimale behandelstrategie voor hun individuele patiënt.

Voorspellen van overleving

Hoofdstuk 2 beschrijft de totstandkoming van een model om de overleving te voorspellen bij patiënten met pijnlijke botmetastasen. Zowel voor patiënten als hun zorgverleners is het belangrijk om de levensverwachting in te schatten, bijvoorbeeld omdat het invloed heeft op behandelbeslissingen. Daarbij is het belangrijk om de tijdsinvestering en bijwerkingen van een behandeling af te wegen tegen het te verwachten effect, de duur van het effect en de duur tot dit effect optreedt. Er bestaan meerdere modellen om de overleving te voorspellen, maar deze werden in de praktijk weinig gebruikt, bijvoorbeeld door de ingewikkeldheid ervan of het gebruik van gegevens die niet standaard beschikbaar zijn bij alle patiënten. Ons doel was om een eenvoudig model te ontwikkelen om de overleving te voorspellen. Hiervoor gebruikten wij de data van de DBMS en, voor externe controle, een recent cohort met patiënten, tussen 2001 en 2010 behandeld met bestraling vanwege wervelmetastasen. De gemiddelde leeftijd in de DBMS was 65 jaar, met een gemiddelde performance status (schaal die functioneren benoemt) van 70 (d.w.z. in staat voor zichzelf te zorgen, maar niet om normale activiteiten te verrichten of om te werken). Patiënten hadden voornamelijk borst- (39%), prostaat- (23%) of longkanker (25%). De mediane en gemiddelde overleving waren respectievelijk 30 en 49 weken. In multivariate analyse bleken geslacht, primaire tumor, aanwezigheid van viscerale metastasen, performance status en scores voor algemene gezondheid en waardering van het leven als voorspellers voor de overleving. Dit model had een C-statistic van 0.72, wat beschouwd wordt als een redelijk voorspellend vermogen. Ons doel was echter om een eenvoudig model te maken. Derhalve werd het model teruggebracht naar twee voorspellers, namelijk performance status en primaire tumor. Het model met deze twee voorspellers had een vergelijkbare C-statistic van 0.71. Nadere analyse toonde aan dat het model de overleving onderschatte. Het model voorspelde het beste voor patiënten met een korte overleving, te weten patiënten met een slechte performance status en een andere primaire tumor dan borst- of prostaatkanker. Dit is de groep waarin inschatting van

de overleving het meest relevant is, om te bepalen of patiënten lang genoeg zullen leven om toe te komen aan de voordelen van de behandeling. De externe dataset bevatte 934 patiënten met een gemiddelde leeftijd van 65 jaar en een gemiddelde performance status van 70. De primaire tumor was ook hier voornamelijk borst- (29%), prostaat- (21%) en longkanker (25%). De mediane en gemiddelde overleving waren respectievelijk 21 en 60 weken. Het eenvoudige model met alleen primaire tumor en performance status had een *C*-statistic van 0.72. Het uiteindelijke model met primaire tumor en performance status kan de overleving redelijk goed voorspellen Verder werd een overlevingstabel gemaakt op basis van beide voorspellers. Deze kan gebruikt worden om inzicht te geven in de overleving van patiënten en artsen in staat te stellen om samen met hun patiënt beslissingen te nemen, onder andere gebaseerd op een adequate inschatting van hun overleving.

Bijwerkingen

De bijwerkingen van bestraling voor pijnlijke botmetastasen zijn vaak mild en vooral afhankelijk van de bestraalde plaats. De helft van de patiënten meldt bijwerkingen, voornamelijk misselijkheid en/of braken. De bijwerkingen hangen af van het bestraalde gebied. Bij patiënten met pijnlijke wervelmetastasen worden twee eenvoudige technieken vaak gebruikt, namelijk een enkelvoudig posterior-anteriorveld (PA, waarbij van achteren naar voren wordt bestraald)) of opponerende anterior-posterior en posterior-anterior-velden (APPA, waarbij zowel van voren naar achteren als van achteren naar voren wordt bestraald). In hoofdstuk 3 worden de bijwerkingen van beide technieken beschreven. In de DBMS werden 343 patiënten behandeld vanwege pijnlijke wervelmetastasen. Zij vulden dertien wekelijkse vragenlijsten in, welke bestonden uit vragen over pijn, medicatie, lichamelijke klachten en KvL. Hierna werden de vragenlijsten maandelijks ingevuld, tot twee jaar follow-up, overlijden of sluiten van de studie. Van de 343 patiënten werden er 250 behandeld met een PA veld en de overige 93 patiënten (27%) met een APPA techniek. Doelgebied waren de lendenwervels (53%) en de borstwervels (34%) of overlappende niveaus (13%). De techniek die toegepast werd was veelal een vaste keuze van de radiotherapie afdeling, en veel minder gebaseerd op individuele patiëntkarakteristieken. Bij aanvang verschilden beide groepen patiënten niet van elkaar, met uitzondering van systemische therapie (chemo- of hormoontherapie). Meer patiënten in de PA groep werden behandeld met systemische therapie dan patiënten behandeld met een APPA techniek (59% versus 43%). De pijnrespons was 74% in beide groepen. Over het algemeen waren de bijwerkingen gering. Patiënten behandeld met een APPA techniek hadden iets meer buikklachten, Ze hadden significant vaker diarree en er was een trend voor meer braken en buikpijn in vergelijking met de PA groep. In multivariate analyse voorspelden locatie en bestralingsschema voor het ontstaan van buikklachten. Voor huidklachten

waren primaire tumor en locatie voorspellend. De gebruikte techniek voorspelde niet voor buik- of huidklachten. Hoewel tegenwoordig ingewikkelder en meer gerichte technieken beschikbaar zijn, zijn de voordelen van deze technieken in deze patiëntengroep nog niet bewezen. Daarbij zijn deze technieken vaak duurder en kosten ze meer tijd voor zowel de patiënt als de bestralingsafdeling. De verwachting is daarom dat de bestudeerde 'eenvoudige technieken gebruikt zullen blijven worden, waarbij geen voorkeur bestaat voor een APPA of PA techniek.

Psychische distress

Psychische distress heeft grote gevolgen voor patiënten en gaat gepaard met symptomen zoals zenuwachtigheid, piekeren, angst en depressie. Bijna de helft van de patiënten met ongeneeslijke kanker ervaart deze symptomen. Hoewel er meerdere interventies bestaan, zoals psychosociale interventies, cognitieve therapie of psycho-educatie, wordt slechts een minderheid van de patiënten daarvoor verwezen. Dit komt mogelijk doordat psychische distress niet altijd wordt herkend. In hoofdstuk 4 beschrijven we de incidentie en het verloop van psychische distress in patiënten in de DBMS. Psychische distress wordt gescoord aan de hand van vragen van de Rotterdam Symptom Checklist over de mate van prikkelbaarheid, piekeren, neerslachtigheid, zenuwachtigheid, wanhopig zijn over de toekomst, gespannen voelen en angst. De totaalscore varieert van 7 (geen psychische distress) tot 28 (maximale psychische distress). Voorafgaand aan behandeling was het gemiddelde niveau van psychische distress 13.4, met een mediaan van 12. Zevenentwintig procent van de patiënten had veel psychische distress (boven de afkapwaarde van 16). Patiënten met veel psychische distress waren meestal vrouw, hadden borstkanker, een slechte Karnofsky performance status en slechte KvL. Het voorspellende model liet zien dat leeftijd, geslacht, performance status, pijnscore en globale KvL voorspellend waren voor psychische distress. Psychische distress was geassocieerd met vrouwelijk geslacht, hogere leeftijd, slechtere performance status, lagere pijnscore en slechtere KvL. In de periode na behandeling bleef de gemiddelde score van psychische distress grofweg gelijk. Bij patiënten met veel distress voorafgaand aan de behandeling nam het gemiddelde niveau van distress af in de eerste weken na bestraling en stabiliseerde daarna rond de afkapwaarde. Bij patiënten die hun vragenlijsten na drie maanden nog retourneerden (waarvan aangenomen mag worden dat die in een betere klinische conditie waren, bleef het beloop van psychische distress vergelijkbaar, hoewel het niveau van distress wat lager lag. Concluderend had een kwart van de patiënten psychische distress voorafgaand aan bestraling. De hoeveelheid distress stabiliseerde na de behandeling rond de afkapwaarde. Screening kan zinvol zijn om patiënten te identificeren die baat kunnen hebben bij interventies, om zodoende hun KvL te behouden of te verbeteren.

Kwaliteit van leven

Gezondheidsgerelateerde kwaliteit van leven (KvL) bestaat uit meerdere dimensies, waarbij fysiek, emotioneel, cognitief en sociaal functioneren meewegen, in relatie tot de gevolgen van ziekte en de behandeling ervan. Hoewel KvL een belangrijk eindpunt is in palliatieve zorg, wordt het slechts gerapporteerd in enkele gerandomiseerde studies naar bestraling bij pijnlijke botmetastasen. De studies die er wel over rapporteren, hebben een aantal tekortkomingen, zoals een korte follow-up of het bestuderen van globale KvL in plaats van in de aparte domeinen. In hoofdstuk 5 bestudeerden en modelleerden we de verschillende domeinen van KvL na bestraling voor pijnlijke botmetastasen. Verder analyseerden we voorspellers voor het beloop van KvL bij aanvang en na de behandeling. Alle KvL items uit de vragenlijsten werden meegenomen, waaruit drie klinisch relevante domeinen werden vastgesteld, namelijk het fysieke, psychosociale en functionele (hoe men functioneert, wat men kan doen) domein. Het niveau van KvL bleek gerelateerd aan de daadwerkelijke overleving. Direct na bestraling verslechterde de fysieke en functionele domeinen en de algemene gezondheid. De laatste twee stabiliseerden hierna en het fysieke domein verbeterde op den duur tijdelijk. Alleen in het psychosociale domein werd een verbetering gezien kort na de bestraling. Na afloop van de behandeling bleef het niveau van KvL in alle domeinen stabiel en toonde een verslechtering enkele weken voor het overlijden. Een hogere pijnscore bij aanvang en gebruik van opioïden was geassocieerd met een slechtere KvL op vrijwel alle domeinen, met wisselende groottes van het verschil. Een slechtere performance status bij aanvang en hogere leeftijd waren geassocieerd met een slechtere functionele KvL. Patiënten met prostaatkanker hadden een slechtere fysieke en functionele KvL in vergelijking met patiënten met andere primaire tumoren, terwijl patiënten met borstkanker een slechtere functionele KvL hadden, hoewel het verschil klein was. Het bestralingsschema was niet gerelateerd aan KvL, behalve in het fysieke domein. Patiënten die behandeld waren met zes bestralingen hadden een tijdelijke verslechtering van hun fysieke KvL de eerste weken na behandeling, in vergelijking met patiënten behandeld met een eenmalige bestraling van 8 Gy. Concluderend stabiliseerde KvL na bestraling voor pijnlijke botmetastasen. Dit kan een effect van behandeling zijn, omdat verslechtering verwacht kan worden wanneer niet behandeld zou zijn. Hoewel het merendeel van patiënten een pijnrespons liet zien, verbeterde de KvL niet noemenswaardig. Dit kan worden verklaard doordat KvL bestaat uit meerdere domeinen. Psychische en functionele problemen hebben ook invloed op KvL. De fysieke KvL wordt, behalve door pijn, ook beïnvloed door andere lichamelijke klachten ten gevolge van de ziekte of de behandeling ervan. Desalniettemin is behoud van KvL een belangrijke uitkomst in deze populatie. In hoofdstuk 6 beschrijven we KvL in relatie tot een pijnrespons. Bij patiënten met een pijnrespons na bestraling zou een betere KvL verwacht worden dan bij patiënten zonder pijnrespons. Daarnaast probeerden we factoren te bepalen die voorspellend zijn voor een pijnrespons, om zo patiënten te kunnen selecteren bij wie het wel of niet zinvol

is om palliatief te bestralen. De data van 956 patiënten uit de DBMS met borst-, prostaat- of longkanker werden gebruikt. De overige 156 patiënten werden buiten beschouwing gelaten omdat deze groep te heterogeen was. De bestudeerde domeinen van KvL waren psychische distress, lichamelijke symptomen, beperkingen in activiteiten, algemene gezondheid en algemene waardering van het leven. Van de 956 patiënten toonden 722 patiënten (76%) een pijnrespons na bestraling, met een mediane duur tot respons van 3 weken. Bij aanvang hadden non-responders (patiënten zonder pijnafname) significant meer beperkingen in activiteiten en een slechtere algemene gezondheid in vergelijking met patiënten die wel een pijnrespons hadden. Er waren bij aanvang geen verschillen t.a.v. de andere domeinen van KvL. Gedurende 12 weken na bestraling was de KvL voor alle domeinen slechter bij non-responders. De meeste KvL domeinen verbeterden bij patiënten met een pijnrespons en verslechterden bij non-responders. Alleen de beperkingen in activiteiten bleven stabiel bij patiënten met een respons, maar verslechterden bij non-responders. De verschillen tussen beide groepen waren kort na bestraling beperkt, maar namen in de loop van de tijd toe en werden klinisch relevant. Bij aanvang waren er verschillen tussen patiënten met een pijnrespons en patiënten zonder. Deze laatste groep had vaker longkanker, uitzaaiingen in lever of longen, een slechtere lichamelijke conditie en kreeg minder vaak systemische therapie. Patiënten met een pijnrespons hadden een mediane overleving van 45 weken, terwijl deze bij patiënten zonder respons 16 weken bedroeg. Het voorspellend model voor een pijnrespons bevatte primaire tumor, leeftijd, performance status, aanwezigheid van uitzaaiingen in lever of longen en het gebruik van opioïden. Borst- of prostaatkanker, jonge leeftijd, goede performance status, geen uitzaaiingen in lever of longen en het gebruik van opioïden, waren geassocieerd met een hogere kans op een pijnrespons. De voorspellende waarde van het model was echter erg laag (C-statistic van 0.55), waardoor het niet bruikbaar bleek voor de klinische praktijk. In analyses per tumortype werd gevonden dat bij patiënten met borstkanker, jonge leeftijd en de afwezigheid van uitzaaiingen in lever of longen geassocieerd waren met een hogere kans op pijnrespons. Bij patiënten met prostaat- of longkanker werden geen aanvullende voorspellende factoren gevonden. Concluderend hadden patiënten met een pijnrespons na bestraling een betere KvL na behandeling dan patiënten zonder pijnrespons. Patiënten met een slechte performance status voorafgaand aan behandeling hadden minder kans om een pijnrespons te ontwikkelen. Het lukte echter niet om een betrouwbaar voorspellend model te maken met betrekking tot pijnrespons.

Effect van leeftijd

Het aantal oudere kankerpatiënten neemt toe door onder andere een langere levensverwachting, het ouder worden van de babyboomgeneratie en betere kankerbehandeling. Oudere kankerpatiënten zijn anders dan jongere patiënten. In het algemeen zijn ze

kwetsbaarder, hebben ze veel leeftijdsgebonden aandoeningen tegelijkertijd en zijn ze in een slechtere lichamelijke en/of cognitieve toestand. Aangezien oudere leeftijd vaak een uitsluitings-criterium is voor studies, is het de vraag of studieresultaten ook op deze groep patiënten toepasbaar zijn. Er is aangetoond dat oudere patiënten anders behandeld worden dan jongere patiënten, bijvoorbeeld dat ze minder vaak behandeld worden met palliatieve bestraling. In hoofdstuk 7 bekeken we het effect van leeftijd op pijnrespons na palliatieve bestraling, om te bepalen of deze behandeling gerechtvaardigd is in oudere patiënten. In de DBMS was 20% van de patiënten 75 jaar of ouder, 35% was tussen de 65 en 74 jaar en 45% was jonger dan 65. Oudere patiënten (≥ 75 jaar) waren vaker man en hadden prostaatkanker. Oudere patiënten waren vaker afhankelijk van anderen m.b.t. de activiteiten van het dagelijks leven: 39% tegenover 26% van de patiënten onder de 65. Er werd geen verschil gevonden in pijnrespons tussen de leeftijdsgroepen: 67%, 74% en 78% in patiënten van respectievelijk ≥75, 65-74 en <65 jaar. Leeftijd was geen onafhankelijke voorspeller voor een pijnrespons. Alle KvL domeinen waren vergelijkbaar tussen de leeftijdsgroepen, met uitzondering van beperkingen in activiteiten. Ouderen hadden bij aanvang al meer beperkingen in activiteiten en dit verschil bleef aanwezig in de follow-up. Concluderend was leeftijd geen voorspeller voor pijnrespons of KvL na palliatieve bestraling voor pijnlijke botmetastasen. Ouderen vonden hun KvL niet slechter dan jongere patiënten. Oudere leeftijd zou dus geen reden mogen zijn om patiënten niet palliatief te bestralen.

Discussie

In hoofdstuk 8 wordt de invloed van de DBMS beschreven op kennis en aanbevelingen uit richtlijnen met betrekking tot palliatieve bestraling bij patiënten met pijnlijke botmetastasen. Voor toekomstige studies is het belangrijk om een vergelijkbare methodologie te gebruiken, om zodoende uitkomsten van verschillende studies en verschillende behandelmethodes met elkaar te kunnen vergelijken. Het gebruik van gelijke uitkomstmaten en definities is erg belangrijk. Aangezien modellen om de overleving in te schatten steeds vaker gebruikt worden in de klinische praktijk, is het belangrijk voor artsen om op de hoogte te zijn van de methodologische eisen waaraan modellen zouden moeten voldoen en zouden ze de bruikbaarheid van een model kritisch moeten kunnen evalueren.
Nieuwe ontwikkelingen in bestraling voor pijnlijke botmetastasen zijn bijvoorbeeld stereotactische bestraling, protonen of de MRI-versneller. Deze nieuwe opties zijn meer tijdsintensief en duurder dan de conventionele behandeling, terwijl de meerwaarde in deze patiëntengroep nog niet is aangetoond. Er zijn bijvoorbeeld geen data die aantonen dat een hogere dosis meer effect heeft op de pijnrespons of de duur van de respons. Voor stereotactische bestraling bij wervelmetastasen zijn momenteel twee gerandomiseerde studies open, die stereotactische bestraling vergelijken met een eenmalige bestraling van

8 Gy. De uitkomsten daarvan zullen erg belangrijk zijn om de plaats van deze behandeling te bepalen bij patiënten met pijnlijke botmetastasen. Voor protonen en de MRI-versneller zijn nog geen studies open die de meerwaarde van deze behandeling onderzoeken.
Ook buiten het gebied van de bestraling hebben nieuwe ontwikkelingen plaatsgevonden, zoals het gebruik van bisfosfonaten. In een gerandomiseerde studie liet 56% van de patiënten hierop een pijnrespons zien. Wanneer bestraling niet mogelijk is, zijn bisfosfonaten een alternatief. Radionucliden geven een pijnrespons in 50-60% van de patiënten, maar zijn niet aangetoond beter of gelijkwaardig aan palliatieve bestraling. Derhalve lijkt hiervoor vooral een indicatie bij patiënten met pijnklachten op meerdere plaatsen als gevolg van botmetastasen. Chirurgische behandeling kan worden overwogen bij patiënten met (dreigende) fracturen en een relatief lange levensverwachting. Lokale chirurgische ingrepen, zoals kyphoplastiek of vertebroplastiek (inspuiten van cement in een wervel), zijn vanwege hun hoge complicatierisico en mortaliteit niet geïndiceerd, temeer omdat er geen data zijn over het effect op pijn. Voor relatief nieuwe en dure behandelopties zoals high intensity focused ultrasound (HIFU) of radiofrequente ablatie (RFA) ontbreken gerandomiseerde studies. Gezien de complexiteit, selectiecriteria en beperkte beschikbaarheid ervan, is het niet de verwachting dat deze behandelingen in de toekomst een plaats zullen hebben in de behandeling van patiënten met pijnlijke botmetastasen. Hoewel de afgelopen jaren meerdere ontwikkelingen zowel binnen als buiten de het gebied van de bestraling hebben plaatsgevonden, is bestraling met een eenmalige bestraling van 8 Gy nog steeds de gouden standaard in de behandeling van patiënten met pijnlijke botmetastasen. Bij bijvoorbeeld (dreigende) fracturen of myelumcompressie, in patiënten met een goede conditie en een relatief lange levensverwachting, kan er een indicatie zijn voor chirurgie.

Pijnflare

Het appendix bestaat uit het studieprotocol van de Dexa-studie. Na bestraling voor botmetastasen ervaart ongeveer 40% van de patiënten een tijdelijke toename van pijnklachten, de zogeheten pijnflare. De definitie van een pijnflare is minimaal 2 punten stijging van de 11-punts pijnscore, zonder afname van pijnmedicatie, of een 25% toename van pijnmedicatie zonder afname van de pijnscore. Een pijnflare heeft een negatieve invloed op KvL en wordt mogelijk veroorzaakt door oedeem rondom het botvlies. Dexamethason zou dit oedeem en dus de incidentie van pijnflare kunnen verminderen. Twee niet-gerandomiseerde studies suggereren dat dexamethason hiervoor effectief is en de incidentie van pijnflare halveert. Een recent gepubliceerde gerandomiseerde studie laat zien dat dexamethason de incidentie van pijnflare vermindert, van 35% naar 26%. Hierin wordt één dosering dexamethason vergeleken met een placebo. Het studieprotocol beschrijft een drie-armige dubbelblind gerandomiseerde multicenterstudie, waarbij twee

armen verschillende doses dexamethason bevatten en de derde arm placebo. Het primaire eindpunt is het ontstaan van een pijnflare Secundaire eindpunten zijn pijn, KvL en bijwerkingen van de medicatie. De benodigde 294 patiënten zijn geïncludeerd in maart 2016. De resultaten worden op korte termijn verwacht.

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Curriculum Vitae

Paulien Westhoff werd op 29 maart 1984 geboren in Zwolle. Na het behalen van haar gymnasiumdiploma aan het Ichthus College in Kampen startte zij in 2002 met de studie geneeskunde aan de Rijksuniversiteit Groningen. In het laatste jaar van haar studie deed ze haar keuzecoschap op de afdeling radiotherapie van het Universitair Medisch Centrum Groningen, gevolgd door een onderzoeksproject onder jonge vrouwen met borstkanker. Na haar afstuderen in 2008 werkte zij drie maanden op deze afdeling als arts niet in opleiding tot specialist. In februari 2009 startte zij met de opleiding tot radiotherapeut-oncoloog in het Universitair Medisch Centrum Utrecht, in samenwerking met het Radiotherapeutisch Instituut Stedendriehoek en Omstreken (opleiders prof.dr. C.H.J. Terhaard en drs. E.J.A. Vonk). Tijdens haar opleiding startte zij een promotietraject en coördineerde de landelijke Dexa-studie, beschreven in de appendix, onder begeleiding van dr. A. de Graeff en dr. Y.M. van der Linden. De resultaten van dit onderzoek zijn beschreven in dit proefschrift. In januari 2015 rondde ze haar opleiding af, sindsdien werkt ze als staflid op de afdeling radiotherapie in het Radboud Universitair Medisch Centrum te Nijmegen.

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