Radiotherapy in bone metastasis : the Dutch bone metastasis study

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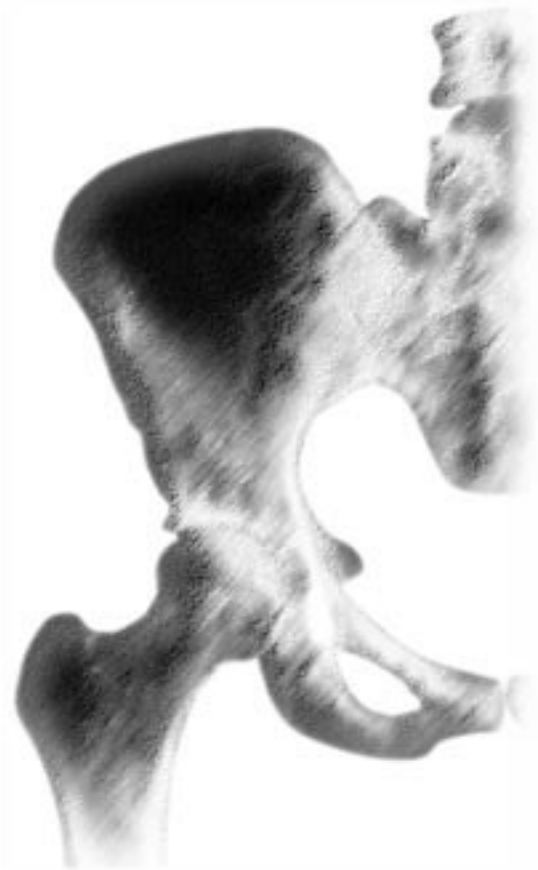

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Introduction and outline

Introduction

Mechanisms of metastasis

In general, all malignant tumors have the potential to metastasize. However, frequency of metastasis and speed of onset after the primary diagnosis differ between the various primary tumors. When the primary tumor grows and becomes vascularized (angiogenesis), invasion of adjacent structures may occur with penetration of blood vessels and lymphatics. Metastasis is the subsequent process in which a tumor cell leaves the primary tumor, travels to a distant site in the body via the haematogenous or the lymphatic circulatory system and establishes a secondary tumor in lymph nodes, vessels or host tissue. The metastasis grows and vascularizes, finally leading to further metastasis from metastases.[1,2]

In bone, tumor growth usually starts in the medullairy cavity, and frequently then grows into the cortex. Many intrinsic biological and micro-environmental factors play a role. [1,2] In the bone marrow, specific growth factors such as insulin-like growth factor (IGF)-1 and transforming growth factor (TGF)-ß facilitate and stimulate the proliferation of tumor cells. Cytokines such as interleukin (IL)–1, IL-6 and tumor necrosis factor (TNF)- α also contribute.[1,3,4] Tumor cells activate the normal bone forming cells, the osteoclasts and osteoblasts, leading to both bone destruction and new bone formation that causes aberrant bone growth. The osteoclasts normally resorb bone during the physiologic process of bone remodeling and repair. When there is a marked increase of osteoclast formation and activity caused by tumor products osteolysis occurs. Following osteolysis there may be a subsequent osteoblastic response, with osteoblasts synthesizing an osteoid matrix, but this is often blunted and sometimes absent.

With bone metastases, tumor cells tend to metastasize to the best vascularized parts of the body. Division of bone metastases over the skeleton is mostly in the red bone marrow of the axial skeleton, and in the proximal ends of the long bones, the ribs, and the vertebral column. Bone metastases in the distal extremities are rare.[5]

The radiographic appearance of a bone lesion is often typical for certain primary tumors. Lytic bony lesions are most common and present in breast, lung, thyroid, renal and gastrointestinal malignancies and in melanoma. Less often, metastases from solid tumors cause an increase in osteoblast activity, leading to excess bone formation (sclerosis). Because the process of synthesis of collagen and other bone proteins is accelerated unnaturally, the newly formed bone is immature and incompletely mineralized. Metastases from prostate cancer especially, but also those from breast, lung, carcinoid and medulloblastoma tumors give rise to these sclerotic lesions.[6]

TABLE 1. COMPARISON OF IMAGING MODALITIES FOR THE DETECTION OF BONE METASTASES

Imaging modality[1]	Anatomic detail	Extent of image[2]	Appearance of bone disease	Causes of false-negative findings	Causes of false-positive findings	Diagnostic sensitivity	Diagnostic specificity	Approximate global charge[3]
SS	No	Whole body	Hot spots	Rapid/pure osteolytic progression	Trauma, inflammation, benign tumor healing	Varies 62-100%[4]	Varies 78-100%	Low ($212.00)
XR	Yes	Local/regional whole body	Lytic, sclerotic, mixed	Bone marrow only Lysis/sclerosis not at treshold for detection Osteopenia	Trauma, inflammation, benign tumor healing	Low 44-50%	Numerical specificity values not addressed	Low ($84.32)
CT	Yes	Local/regional[5]	Lytic, sclerotic, mixed for bone, higher attenuation for marrow	Lysis/sclerosis not at treshold for detection	Trauma, inflammation, benign tumor healing	High 71-100%	Numerical specificity values not addressed	Moderate (thoracic $291.02; abdominal $282.76 without contrast)
MRI	Yes	Regional[5]	Low or higher intensity signal on T1/T2 scans	Lesion only in the cortex	Edema	High 82-100%	High 73-100%	Moderate (cervical spine $521.33; thoracic spine $568.86 lumbar spine $562.87 without contrast)
PET	No	Whole body	Hot spots	Lesion only in the cortex	After chemotherapy	Varies 62-100%	High 96-100%	High ($2097.22)
SPECT	No	Local	Hot spots	Same as SS	Same as SS	High 87-92%	High 91-93%	Moderate ($285.29)

[1] SS= skeletal scintigraphy, XR= plain radiography, CT= computed tomography, MRI= magnetic resonance imaging, PET= positron emission tomography, SPECT= single photon emission computed tom

[2] Terms are defined as follow: whole body= the entire body is studied at one time with one image; regional= large anatomic area studied at one time with one image: and local= focal or sm studied at one time with one image.

[3] Estimates are based on Medicare fee schedules for Harris County, Texas, USA. Low= less than $ 250; moderate= $ 250 to $ 999.99; high= more than $ 1000. Values are given in U.S. dollars.

[4] Although the ranges of sensitivity and specificity values for SS vary, in most reports SS is regarded as a highly sensitive but poorly specific modality.

[5] Newer applications of CT and MRI may be useful for obtaining whole body images in a time, but the cost of central axial skeletal imaging remains high.

Epidemiology

In the Netherlands, every year around 66.000 new patients are diagnosed with cancer.[7] In approximately half of these patients, metastatic spread of tumor cells occurs during follow up. For the patient this signifies a catastrophic event: it means that the malignant process is incurable and treatment is no longer directed towards cure. Only optimal palliation of disease-related symptoms is achievable. Each year, around 37.000 patients in the Netherlands die of metastatic cancer. [7] Bone is the third most frequent site of tumor metastasis, after other localizations as lung and liver. The malignant tumors that frequently metastasize to the skeleton also affect patients most commonly: breast cancer, prostate cancer and lung cancer. In the Netherlands, every year approximately 10.000 persons are diagnosed with breast cancer, 7.000 persons with prostate cancer, and 9.000 persons with lung cancer.[7] The incidence and prevalence of bone metastases in cancer patients are difficult to determine with accuracy: studies report a frequency of 10-47% of all patients with breast cancer developing metastases to the bone during their illness. [8-10] In autopsy studies, more than 70% of breast cancer patients had tumor deposits in the bone.[11,12]

Duration of survival after the clinical manifestation of bone metastases depends on whether the metastasis is a solitary lesion or multiple metastases exist throughout the skeleton. If a patient also has visceral metastases, the prognosis is generally worse. In addition, the type of primary tumor affects the disease outcome. Patients with breast cancer or prostate cancer may have a prolonged survival, sometimes stretching over several years. Improvements in systemic therapy and the hereditary relatively long clinical course of these primary tumors underline this observation. However, the majority of patients die within 5 to 12 months after clinical manifestation of the bone metastases.[13] For the treating physicians, predicting the chance of occurrence of metastasis is a major factor when deciding on treatment, such as adjuvant systemic therapy and/or radiotherapy. In addition, when there is a high probability of metastasis in a patient, the choice for disabling surgical procedures maybe abandoned in view of the life expectancy of the patient.

For the radiotherapy department and its employees, care for patients with painful bone metastases comprises a large percentage of the daily workload: up to 10-15%.

Imaging

Radiographic imaging is an essential part of the management of bone metastasis. There are several imaging modalities available. Recently, Hamaoka et al published an overview of current practice. [14] Table 1 comprises the advantages and disadvantages of the several modalities. In general, if a patient has circum-

scribed local pain plain radiography is a valuable tool.Whole body skeletal scintigraphy is most commonly used for screening to detect bone lesions, because it is considered sensitive in visualizing both osteolytic and osteoblastic bone metastases. The findings of scintigraphy however reflect the metabolic reaction of bone to several disease processes, including trauma or inflammation. It has a lower specificity and higher false positive rate than plain radiography. Therefore, other modalities, such as plain radiography, but also computed tomography (CT) or magnetic resonance imaging (MRI) should always be used to characterize these lesions, including any soft tissue components and to assess the risk of fracture. The fusion of positron emission tomography (PET) and CT has the potential for sensitive detection, however, PET technology is not widely available yet. Few studies have been done on the use of single photon emission computed tomography (SPECT) in bone metastases.

Clinical implications and treatment modalities

For the patient, bone metastases may cause a range of complications, varying from mild to severe pain at the site of the metastasis, pathological fracturing of bone, spinal cord compression or nerve root compression syndromes, and hypercalcemia. The intensity of these symptoms is mostly dependent on the localization and extent of the lesion in the skeleton.

A variety of palliative treatment modalities is available for bone metastases. The majority of treatments are directed towards optimum palliation with minimum treatment related morbidity. Choice for a certain treatment is dependent on the complaints and life expectancy of the patient, and whether co-morbidity exists that opposes this treatment. Other influencing factors are the localization of the metastasis in the skeleton, and whether the metastasis is solitary or multiple bone lesions exist.

1. Pain

The mechanisms that underlie the sensation of pain caused by metastasis are poorly understood. The presence of pain does not seem to be correlated with the type of tumor, location, number or size of the metastases. [15] It is thought that when tumor cells grow, the periosteum, which is the highly innervated connective tissue sheath that covers the external surface of the bone, is stretched. Pain receptors (nociceptors) are subsequently activated, and may show sensitization, which is manifested as a decreased threshold of activation after injury and the emergence of spontaneous activity. [16,17] This may explain why some lesions cause such a deep, dull, aching sensation without even the least contact.[6] In addition, chemical mediators of pain such as prostaglandins are thought to play a role. [15] Treatment strategies are focused on these above mentioned mechanisms.

Analgesic drugs that inhibit certain pathways are generally available and relatively simple to administer. Most analgesics are effective in treating pain, although some patients respond poorly. Depending on the quantity and duration of analgesics intake the patient may suffer from serious side effects. For example, opoids cause nausea, constipation and drowsiness. Non-steroidal anti-inflammatory drugs may cause gastrointestinal ulceration with subsequent bleeding. If pain is caused mainly by edema subsequent to metastatic involvement, steroids such as dexamethasone may also be helpful. Steroids should be administered as shortly as possible, because they may cause drug dependency and induce diseases like diabetes and Cushing syndrome.

For localized pain, radiotherapy is a well-accepted treatment modality with 60-80% overall pain relief reported. [18-20] The precise analgesic effect of radiotherapy remains unknown. Because the onset of pain relief is often rapid (i.e., within days), it is not likely to link the anesthetic effect to tumor shrinkage alone.[15] More likely, a response mechanism through chemical mediators such as prostaglandins is the cause of less pain. Dependent on which part of the body is irradiated, treatment volume and total radiotherapy dose, transient side effects of radiotherapy that may occur are tiredness, flare up of pain, skin reactions or gastrointestinal complaints such as nausea or diarrhea. In general, palliative radiotherapy is a relatively safe treatment that can be applied repetitively.

Another local treatment for pain is a surgical intervention. For example, if a patient suffers from painful osteolytic metastases in the femur or humerus with cortical involvement and rising instability, osteosynthesis may cause immediate relieve of pain and prevent pathological fracturing. The treating physician should weigh the morbidity of a surgical procedure against the stabilizing capability of prophylactic surgery. Relatively new minimal invasive procedures such as vertebroplasty in osteolytic spinal metastases could be appropriate to treat back pain. [21,22] With vertebroplasty, polymethylmethacrylate is injected into the vertebra to immediately strengthen the affected bone.

A relatively new treatment for painful bone metastases is radiofrequency ablation (RFA), which utilizes a high-frequency alternating current that is passed from the needle electrode into surrounding tissue, resulting in frictional heating and necrosis. A decrease of pain in 95% of treated patients was reported with this technique.[23]

If a patient has diffuse pain arising from numerous metastases, a systemic treatment is considered more beneficial than a local treatment, provided of course that the primary tumor is sensitive to systemic therapy. Mostly, patients with breast cancer or prostate cancer benefit from these treatments. A variety of effective chemotherapeutic agents, hormonal therapies [24] and

radionuclides[20,25] is available. In addition, regular infusions with potent inhibitors of osteoclastic bone resorption such as bisphosphanates decrease the number of skeleton related events and bone pain in patients with breast cancer and prostate cancer ,[20,26-28] as well as in patients with lung cancer and other solid tumors.[29]

2. Pathological fracturing

Progressive involvement of the bone cortex weakens the axial strength of the bone and gives rise to instability. To minimize the chance of a pathological fracture in weight-baring bones, it is important to search for lesions at risk of fracturing and treat them assertively. Unfortunately, it is difficult to predict which lesions are at risk, using radiographic imaging and clinical information. Current indications for prophylactic treatment come from retrospective studies and have not been clearly defined. Prediction of fracturing based on lesional characteristics is therefore considered to be not very accurate and needs further refining.[30,31]

However, large or impending lesions of the femur or humerus may require prophylactic osteosynthesis to prevent disabling fracturing. [30] An advantage of elective surgery is that patients with a relatively good performance are easier to operate with less morbidity and even mortality than after pathological fracturing has occurred. Alternative treatments for impending lesions in inoperable patients are multiple fraction radiotherapy or regular infusions with bisphosphanates to induce remineralization of the affected bone. [20,26-29,32] However, the strengthening effect of these non invasive treatments will take weeks to months.

Pathologic fractures can occur spontaneously or following only trivial injury, particularly in osteolytic lesions. Even in bed-ridden patients long bones tend to fracture due to torsional forces when patients turn in their beds.[33] Fracturing mostly arises in weight bearing bones, such as the femur, humerus and vertebrae of the spinal column. Dependent on the localization of the fracture, the patient faces direct immobilization with considerable pain and morbidity. Pathological fractures in long bones require stabilizing osteosynthesis to restore mobility of the patient and to treat their pain. [30] Mostly, radiotherapy is administered afterwards to induce remineralization of the fractured bone and stabilize the osteosynthetic prosthesis. [32,34]

3. Spinal cord or nerve root compression syndromes

If bulging tumors in the vertebrae of the spinal column compress nerve roots or the spinal cord, neurological symptoms may occur, ranging from neuropathic pain and cauda equina syndromes to total paraplegia. Due to pathological fracturing of the vertebrae, bone fragments compressing nerve roots or the spinal cord may cause the same symptoms. In general, if a patient expresses neurological complaints, an emergency MRI should be made to locate where the spinal cord is compressed in order to start treatment as soon as possible. [35] Although Harrington provided a classification system based on clinical symptoms to choose the appropriate treatment for each patient presenting with a spinal metastasis,[36] there is no consensus among different physicians on the most appropriate treatment or sequence of treatments for patients with spinal metastases.

In general, radiotherapy in combination with high dose steroids can be a meaningful treatment in spinal cord or nerve root compression syndromes.[35,37-41] Decrease of symptoms after radiotherapy doses of 16 - 24 Gy was reported in 10 - 90% of the patients, depending on the severity and duration of the pretreatment neurological symptoms. [35,37-40] A surgical procedure to the spine should be considered if bone fragments endanger the spinal cord, if neurological symptoms do not respond to radiotherapy, or if tolerance of the spinal cord to radiotherapy has been reached. [36] Several surgical techniques were developed ranging from minimal invasive methods such as palliative laminectomy to extensive procedures such as radical en-bloc resection. Choice for a surgical technique depends on expected survival, treatment-related morbidity and outcome after treatment. In general, the more extensive the surgical technique, the more prolonged the palliative effect, however, the more extended the treatment related morbidity for the patient. [36]

4. Hypercalcemia

In patients with mostly osteolytic lesions, rising of blood serum calcium due to an increase in bone resorption may cause a variety of symptoms relating to the degree of serum calcium elevation and the rapidity of its rise. [42,43] Mild hypercalcemia (serum calcium level < 2.88 mmol/L) usually results in few symptoms. Polyuria and polydipsia may occur because of decreased renal concentrating capacity (nephrogenic diabetes insipidus). Dyspepsia may be caused by calcium-mediated increased gastrin secretion. Vague symptoms of depression or mild cognitive impairment sometimes occur. Symptoms become more manifest when hypercalcemia is moderate (serum calcium level 2.88 to 3.5 mmol/L), apathy, fatigue, muscle weakness, anorexia, nausea, and constipation can occur. Severe hypercalcemia (serum calcium level > 3.5 mmol/L) is associated with further progression of the previously mentioned symptoms as well as dehydration, abdominal pain, vomiting, lethargy, and coma. Although bisphosphanates in combination with rehydration are effective in treating hypercalcemia, its appearance is an ominous sign. The syndrome is eventually fatal, with some patients dying within weeks to months.

Although, in general, small lesions give few symptoms and large lesions may cause severe problems, there is no linear correlation between size of the metastasis and severity of the symptoms. It is therefore important to monitor patients carefully and choose diagnostic imaging tools and subsequent treatments individually for each patient. In addition, patients and their relatives should be informed on the symptoms of bone metastases. During their illness, many patients receive one or more different treatments, sometimes concomitantly or consecutively. Most favorable, the treating physicians and healthcare workers cooperate in a multidisciplinary setting to discuss the right choice of treatment for each patient, taking into account life expectancy and expected outcome after palliative treatment.

The Dutch Bone Metastasis Study

In the Netherlands in the seventies and eighties, patients with painful bone metastases were usually treated with protracted regimens. Dose schedules ranged from 24 Gy in 6-8 fractions or 30 Gy in 10-15 fractions for the majority of patients, to 40-50 Gy in 20-25 fractions for patients with an expected prolonged survival. Only patients with a poor performance status were given few fraction or single fraction regimens, which were considered less time consuming, but also less effective.

Before the Dutch Bone Metastasis Study (DBMS) started of in March 1996, effectiveness of radiotherapy for painful bone metastases had already been the subject of interest in several retrospective and prospective studies, [44-48] and in several prospectively randomized trials. [49-55] In these studies, different dose schedules were applied ranging from protracted regimens to few fraction or single fraction schedules in patients with various types of primary cancers. The underlying thought of few fractions or single fraction radiotherapy versus more protracted regimens was that if both treatments were iso-effective, then fewer fractions would be more beneficial to both the patient and the radiotherapy department. Of course, it would spare the patient, with only a limited prognosis, weeks of painful and tiring visits to the hospital. For the already crowded radiotherapy departments an economic use of resources was anticipated. In addition, societal costs were expected to be considerable less with single fraction regimens.

In most of the studies, no clear dose-response relationship could be found between the various dose schedules. Therefore, the majority of the papers concluded that single or few fraction radiotherapy was equally effective as multiple fractions in reducing pain. However, there was much debate whether conclusions drawn from these studies were applicable in all patients presenting with painful bone metastases.[31,56-58] Firstly, in these studies, follow up of patients was often limited or the patients' compliance poor. Secondly, criticism was aimed at the heterogeneous designs of the studies with small patient groups and various methods of pain assessment making comparison difficult, if not impossible.[13] In addition, the studies included selected groups of patients and no answer was formulated on whether patients with a more prolonged survival would perhaps only benefit from a higher total dose of radiotherapy. Quality of life issues were not studied commonly. In addition, trial data were sometimes multi interpretable. An example of different interpretations of data was the two analyses of the RTOG 74-02 study by Tong et al and by Blitzer. The first paper by Tong et al concluded that short course radiotherapy with doses of 15 to 20 Gy in one week was as effective as high dose radiotherapy (30 to 40.5 Gy in 2-3 weeks).[49] A reanalysis by Blitzer concluded the opposite: protracted dose fractionation schedules were more effective than short course schedules. [56] Lastly, most radiation oncologists just could not believe that single fraction radiotherapy was as good as multiple fractions for treating pain. Retreatment rates were more frequent after single or short term radiotherapy as compared to multiple fractions, underlining this disbelief. As a consequence of all these uncertainties, physicians throughout the world were reluctant to implement single fraction radiotherapy as the standard therapy for the majority of patients with painful bone metastases. [59-61]

In the Netherlands, in the early nineties, there was still no consensus on how to treat patients with painful bone metastases. Although the single dose regimen was applied more often, dose schedules ranged from a single fraction of 6 or 10 Gy to 30 or 40 Gy in multiple fractions. In order to reach a consensus, the large prospectively randomized Dutch Bone Metastasis Study was started in March 1996 on the effectiveness of a single fraction of 8 Gy versus 24 Gy in 6 fractions. In the study design a few unique elements were incorporated, distinguishing this study from the published papers so far: a registration study was started concomitantly to include all ineligible patients. Objective of this registration study was to see if randomized patients were a representative sample of the population of patients with bone metastases. In addition, patients who were considered to have a more favorable prognosis were separately randomized to evaluate the long-term palliative effect of both treatment schedules in these patients. Seventeen out of the 21 radiotherapy institutes in the Netherlands participated in the trial. Between March 1996 and September 1998, 1171 patients were entered for randomization into the study, and 2913 patients were entered into the registration study. Follow up continued for 2 years and consisted of frequent patient-based questionnaires with questions on pain, treatment side effects, analgesic consumption and quality of life.

Outline

In this thesis, a variety of the questions that remained unanswered in the introduction is addressed concerning the role of radiotherapy in the treatment of patients with painful bone metastases from solid tumors. The data for the analyses came from the patients enrolled into the prospectively randomized Dutch Bone Metastasis Study.

Chapter 2 comprises an editorial, which discusses the reluctance among radiation oncologists to accept the single dose regimen as a meaningful therapy. Among others, type of reimbursement may be a contributing factor in deciding on palliative radiotherapy treatment schedules.

In **chapter 3**, the first year global outcome of the DBMS on the treatment of patients with painful bone metastases with radiotherapy is presented. A single fraction of 8 Gy was given to 579 patients and 578 patients received 24 Gy in six fractions. We report on survival, response to pain, treatment side effects, number of retreatments, overall quality of life and changes in analgesic consumption. In addition, all patients that entered the registration study are discussed in comparison with the randomized patients.

During follow up, 16% of the DBMS patients received a second radiotherapy treatment, with more retreatments after a single fraction (24%) than after multiple fractions (6%) (P< 0.001). In **chapter 4** we present the results of a reanalysis of the database which was carried out in alignment with the 2002 International Bone Metastases Consensus Working Party guidelines. [62] These guidelines were published after publication of the first paper of the DBMS and recommended to calculate response separating the effect of retreatment and analgesics intake. Chapter 4 discusses the total response percentages including and excluding the effect of a possible retreatment during follow up. In addition, effectiveness of retreatment and factors influencing the choice whether to retreat or not are discussed.

The palliative effect of both treatment schedules in patients with an observed long-term survival is discussed in **chapter 5**. One year after randomization, 28% of the patients were alive within the DBMS. We also report on survival and prognostic factors for survival in patients with painful bone metastases.

Patients with metastatic lesions with an expected high risk of fracturing had been excluded from participation into the DBMS. However, during follow up 35 fractures occurred with significantly more fractures after 8 Gy single fraction (4%) than after multiple fractions (2%) (P< 0.05). **Chapter 6** describes the outcome of a study on pre-treatment fracture risks of the femur. We analyzed if 14 fractures that occurred in the femur were caused by an insufficient total dose or merely because larger lesions had been present in the single dose arm. The pre-treatment conventional radiographs of 102 patients with a total of 110 femoral metastases were analyzed on lesional sizes and characteristics.

Conventional risk factors for fracturing of osseous metastases in the femur were evaluated for their predictive values in the 102 patients with a femoral metastasis treated within the DBMS. Whether accurate foreseeing of a pathological femoral fracture is feasible is the subject of **chapter 7.**

For patients with spinal metastases, surgery is generally considered an accepted treatment modality when bone fragments endanger the spinal cord or when radiation tolerance has been reached. However, three studies that were based upon retrospective data [63-65] advocated surgery for the majority of patients with spinal metastases: not only in patients with a relatively good prognosis, but also in patients with a limited life expectancy. Furthermore, patients who were also candidates for radiotherapy received a surgical procedure. In **chapter 8** we report on survival and effectiveness of radiotherapy in 342 patients with a spinal metastasis. A scoring system was developed to predict survival and to use as a tool to decide on the type of palliative treatment.

The socio-economic impact of the two palliative regimens single versus multiple fraction radiotherapy for painful bone metastases is assessed in a cost-utility analysis in **chapter 9**. In this analysis, effectiveness is measured by quality-adjusted life expectancy, i.e. the overall valuation of health of the patients in the study. The difference in this quality-adjusted life expectancy was compared with the difference in total costs to society, including medical costs of radiotherapy, other costs of health care utilization, and costs incurred by the patients. In this chapter, willingness-to-pay is introduced as a tool to decide which treatment to apply for painful bone metastases.

In **appendix 1**, the original paper by Steenland et al, [66] on which chapter 3 was based, is added in order to bundle all publications on the Dutch Bone Metastasis Study.

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Impact of randomized trial-outcome in the treatment of painful bone metastases; patterns of practice among radiation oncologists. A matter of believers versus non-believers?

Editorial

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