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Criteria for Palliation of Bone Metastases – Clinical Applications

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FOREWORD

Bone metastases are a frequent complication of cancer. It is estimated that they arise in 14–70% of all tumour patients, while it was reported that they occur in 70–85% patients in autopsy material. Although they may arise from any primary malignant tumour, certain tumours such as breast, prostate, lung, thyroid, kidney and myeloma have a predilection for a spread to bone. Bone metastases frequently cause pain, but there are also clinical situations with bone metastases causing no pain at all.

The overall importance of the problem of bone metastases is well recognized by the fact that each year hundreds of thousands of cancer patients develop bone metastases. For example, more than 100 000 new patients develop this condition in the United States of America, although the prevalence is estimated to be double the number of new cases. While it is virtually unknown how many cancer patients in the developing countries develop bone metastases, it is not unrealistic to expect that these figures largely surpass those coming from the developed countries. The reason is simply that more patients in the developing countries are diagnosed as having locally advanced or metastatic cancer that will eventually widely disseminate, including bone metastasis as well. Furthermore, at least some of the cancer patients may survive prolonged periods of time. They can also develop earlier and more severe symptoms than patients harbouring other types (locations) of metastases, emphasizing the importance of the overall problem of painful bone metastases. In addition, there is a big socioeconomic problem of bone metastasis, burdening health care systems worldwide, while having continuous adverse psychological effect on both patients and their families.

The management of patients with metastatic bone pain must be a multidisciplinary approach and includes the use of analgesia, radiotherapy, surgery, chemotherapy, hormone treatment, radioisotopes and bisphosphonates. Analgesia, with non-steroidal anti-inflammatory drugs, is the first option in most patients, progressing to stronger opioids as the intensity of pain rises. These drugs produce unwanted side effects such as nausea, sedation, and constipation. Local external radiotherapy or surgery can be used for localized metastatic disease and hemibody radiotherapy might be suitable for patients with disease extending to one region of the body. In patients with widespread painful bone involvement, bone-seeking radiopharmaceuticals provide a promising pain-control strategy.

This TECDOC should be seen as a guide and useful resource both for researchers and practitioners alike in both radiation oncology and nuclear medicine fields. The IAEA has put special emphasis on the issue of bone metastasis in the research field of cancer. Recent coordinated research projects have shown that it is an important issue to be addressed through clinical trials setting the best need of developing countries.

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EDITORIAL NOTE

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CHAPTER 1
INTRODUCTION

1.1. Incidence

Metastatic bone cancer is a common and severe complication in advanced disease. It develops in up to 70% of patients with prostate cancer and breast cancer, and in up to 30% of those with cancers of the lung, bladder, and thyroid. The major complications associated with bone involvement are severe pain, spinal cord compression, and pathological fracture — all of which restrict mobility and sleep, greatly reducing the patient's quality of life. The scale of the clinical problem is substantial, since cancers of the prostate, breast, and lung account for about 45% of cancers in all sites. Bone lesions are commonly radiographically classified as osteolytic, when bone destruction arises by the action of osteoclasts (as seen in patients with breast cancer), or osteoblastic, which predominates in prostate cancer and is characterized by sclerosis. However, a mixed pattern is common in many lesions, and marker studies suggest that both resorption and formation occur simultaneously.

1.2. Pathophysiology of bone pain

The pathophysiology of bone metastasis and related complications is complex [1.1]. Normal bone undergoes continuous remodeling that is essential to maintain mechanical function. The process is performed by a multicellular unit formed by 2 different cell types, osteoclasts and osteoblasts. Osteoclasts resorb bone, whereas osteoblasts replace bone [1.2]. Systemic factors — such as the parathyroid hormone, local osteoclast-activating cytokines, and growth factors — contribute to the process [1.3]. During bone resorption, growth factors and mineral ions are released from the bone matrix. When bone metastases occurs, a cycle of signalling takes place that results in increased osteolytic activity. Tumour- derived factors stimulate osteoclast-mediated bone resorption, whereas the growth factors released from the bone matrix stimulate the tumour cells to grow and secrete additional cytokines. This leads to osteopenia and increased risk of developing fractures and, when lesions are in vertebrae, spinal cord compression. The calcium released from the bone matrix in the course of this process can lead to the hypercalcemia of malignancy, a serious metabolic condition. Skeletal metastasis is a multifactorial process in which several biologic processes play a role leading to interaction between host and tumour cells. Cellular invasion and migration, cell matrix adhesion or cell-to-cell adhesions, interaction with endothelial cells, regulation of growth factor, and stimulation of osteoclasts and osteoblasts are thought to contribute to development of skeletal metastasis. Cadtherins, integrins, imuunoglobulins, selectins, and CD44 are some of the molecules implicated in loss of cellular adhesion that causes cell matrix detachment, invasion, and migration. Several isoforms of CD44, an adhesion molecule that binds hyaluronate, have been associated with lymphatic spread of the tumours and are expressed in breast and colon cancers. P selectins bind to a wide range of carcinoma cells, including breast, colon, and lung. Interaction with the endothelial cells leads to local arrest or further migration of the tumour cells. Platelet fibrin thrombi and inflammatory cytokines lead to adhesions and arrest of the tumour cells, whereas chemotactic factors lead to increased mobility of tumour cells. Invasiveness is mediated by several enzyme systems, including serine proteases, of which matrix metalloproteins and urokinase plasminogen activation system are thought to be most important. Cellular motility is critical for tumour cells to develop distant metastasis. Motility is mediated by several factors, including: growth factors, hyaluronians, components of matrix, and host- or tumour-secreted factors. Cytokinins such as autotoxin and hepatocyte growth factor are also implicated in inducing cell motility [1.4]. Pain from bone metastasis is of

variable intensity and intermittent at onset but progresses to continuous low level pain with episodes of breakthrough pain, which later becomes chronic pain. Mechanical allodynia, in which normal nonpainful activity such as coughing and gentle limb movements can also be perceived as painful, can occur leading to significant limitation of activity. Bone pain is thought to be distinct from neuropathic or inflammatory pain, where there is upregulation of the glial fibrillary acidic protein in the spinal cord indicating astrogliosis. The exact mechanism of cancer pain is unknown and it is postulated that the pain may be due to the presence of tumour in the bone. Treatment with bisphosphonates supports the thought that osteolysis leads to bone pain, which is linked to the number and extent of osteoclastic activity. Bone cancer pain is also thought to occur due to sensitization of the nervous system. Sensory information from peripheral tissues is transmitted to the spinal cord and brain by primary afferent sensory neurons, nociceptors that detect stimuli that are perceived as harmful and convert into electrochemical signals that are transmitted to the central nervous system. Tumours secrete a variety of factors that sensitize or directly excite primary afferent neurons, causing the sensation of pain. Receptors for many of these factors are expressed by primary afferent neurons. Peripheral sensitization leads to increased release of substance P from nociceptors, even with minor stimulation. Sensitization also occurs centrally in the dorsal horn of the spinal cord, which leads to allodynia and hyperalgesia. The spinal cord may show marked astrocytosis, increased expression of c-Fos (a general marker of neuronal activity), and a peptide — dynorphin. Other factors that may contribute to the activation of sensory neurons, is the lower intracellular and extracellular pH of solid tumours, which can also cause pain in cancer patients. It is also thought that tumour growth may entrap and injure nerves, causing neuropathic pain.

1.3. Clinical presentation

Clinical presentation of bone metastasis includes pain, pathologic fracture, hypercalcemia and spinal instability with cord compression.

1.3.1. Pain

Pain is the most common presenting symptom with either osteolytic or osteoblastic lesions. Mechanical pain usually is associated with bone loss in lytic lesions; however, blastic lesions may weaken the bone sufficiently through the loss of structural intregity to cause functional pain. The presence of and severity of pain is not correlated with the tumour type, location, number or size of metastases, or the gender or age of the patient. Pain develops gradually during a period of weeks or months, becoming progressively more severe. It is often poorly localized and has been described as a deep, boring sensation that aches or burns and is accompanied by episodes of stabbing discomfort, often worse at night. The intermittent exacerbations of pain can occur spontaneously or relate to activity such as movement, weight bearing or position. In general, it can be divided into 2 types of pain according to the presenting symptoms or mechanism of the disease. In terms of symptoms there may be ‘continuous pain’ which is typically a dull aching pain, and ‘incident pain’ is a movement evoked or breakthrough pain. The pain mechanism may be primary or secondary pain. ‘Primary pain’ is caused by bone resorption and disrupts skeletal architecture causing microfracture, stretching of periosteum by tumour expansion, nerve entrapment and bone collapse. ‘Secondary pain’ is caused by releasing of algesic chemical mediators, nerve root infiltration or compression and reactive muscle spasm. Well-tolerated, repeatable, effective treatments for bone pain are necessary to optimize quality of life for patients with this condition.

1.3.2. Pathlogical fracture

Pathological fracture may be the first sign of bone metastasis in some cases. The incidence of pathological fracture is uncertain. Breast cancer is the most common primary site. The mechanism is related to the destruction of cortical bone which reduces its load-bearing capabilities, resulting in trabecular disruption and microfractures and subsequently in total loss of bony integrity. It can occur spontaneously or following trivial injury, particularly in osteolytic metastasis, most frequently in the vertebral body and the proximal end of long bone. The probability of developing fracture increases with the duration of metastatic involvement and in therefore most likely cases with disease confined to bone who have a relatively good prognosis. Because the development of a fracture is so devastating to the cancer patient, increased emphasis is now being placed on attempts to predict which metastatic sites will be at risk of fracture, the use of prophylactic surgery, radiation and administration of bisphosphonates.

1.3.3. Hypercalcemia

Hypercalcemia is defined as an elevated plasma ionized calcium. This occurs frequently in patients with bone metastases from myeloma, and breast, lung and prostate cancers but may be seen with any primary site including lymphoma where it is characteristically associated with the HTLV1 associated form. Symptoms usually occur only once the calcium value exceeds 3 mmol/l and their severity correlates with higher values. It is associated with pain, nausea, vomiting, anorexia, constipation, weakness, dehydration and polyuria, mental disturbances, and confusion. Hypercalcemia usually occurs in the case of widespread osteolytic lesion and decrease in activity because of pain with associated disuse osteolysis can exacerbate the hypercalcemia. In most cases the mechanism is due to one or more systemic factors produced by tumour cells, such as parathyroid hormone related protein, stimulating osteoclastic bone resorption and increased renal tubular calcium resorption. Thus hypercalcaemia may be seen with few or no detectable bone metastases where the parathormone related peptide production is from tumour cells at the primary site. Hypercalcemia is associated with hypercalciuria and polyuria and plasma volume depletion leads to dehydration and poor renal function (poor renal perfusion, reduced glomerular filtration, compromised calcium excretion) which results in a further increase of plasma calcium. The frequency of hypercalcemia may decrease with more widespread use of bisphosphanates.

1.3.4. Spinal instability with cord compression

Spine is the most common site of bone metastasis, so spinal instability and neurologic abnormalities are common. Spinal cord compression can leads to loss of ambulation and significantly impact on quality of life. The onset of progressive neurological symptoms is often insidious. Vague complaints of back pain, leg weakness, and dysaesthesias should be noted and investigated because early detection and intervention determine the functional outcome. Unilateral radicular pain can occur with lesions in cervical or lumbosacral spines, and may be bilateral when originating in the thoracic spine. Pain is exacerbated by recumbency, neck flexion, straight leg raising, coughing and local pressure, and may be relieved by sitting up or lying absolutely still. Weakness, sphincter impairment and sensory loss are uncommon at presentation, but they can develop rapidly as the initial cord oedema is replaced by the mechanical compressive phase. The keys to successful rehabilitation are early diagnosis, high dose corticosteroids, and rapid assessment with urgent referral for either decompression and spinal stabilization or radiotherapy. Neurologic recovery is unlikely if the spinal compression is not relieved within 24–48 hours.

1.4. Diagnosis of bone metastasis

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 [1.15]. Table 1.1 shows the advantages and disadvantages of the several modalities. In general, if a patient has circumscribed 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, including not only plain radiography, but also computed tomography (CT) or magnetic resonance imaging (MRI) should 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 and is also not specific for bone metastases but will demonstrate any area of increased metabolic rate and glucose turnover. Few studies have been done on the use of single photon emission computed tomography (SPECT) in bone metastases.

1.4.1. Imaging

The diagnosis of bony metastasis from various cancers is usually made on the basis of localized skeletal symptom and tenderness, detailed history, and the radionuclide bone scan. Increasing serum levels of alkaline phosphatase, procollagen terminal peptide as well as certain tumour markers, such as PSA in prostate cancer patients and CA27.29 or CA15.3 in breast cancer patients, often suggest the presence of recurrent/metastatic disease. Bone scan using ^{99m}Tc-labeled phosphate compounds generally demonstrates multiple focal areas on increased uptake related to osteoblastic reaction, that is very sensitive but non-specific. Therefore, pure osteolytic metastatic lesions may not be revealed on the radionuclide bone scan. Conversely, single focal areas of increased uptake (often observed especially in elderly patients during follow-up) may cause interpretation problems for discriminating benign versus malignant lesion. In certain case of difficult differential diagnosis, CT guided biopsy is advised. Purely lytic lesions are better identified on skeletal X ray, CT, MRI, high-resolution PET with ^{18}F-fluoride, or tumour-specific nuclear scans using ^{18}F-FDG, ^{123}I-MIBG, or ^{111}In-Octreotide. MRI is most useful for detecting metastatic lesions in the bone marrow, brain, spinal canal (including heptomeninges as well as nerve root entrapment), and soft tissues. Multi-slice and multi-formatted CT is particularly helpful in identifying the destructive process of bony metastases, impending fracture and vertebral collapse. MRI and CT with contrast agents are frequently used for differentiating bony metastasis from benign bone lesions. The radionuclide bone scan is absolutely necessary to document metastatic lesions at the sites of pain, for better selecting patients expected to derive clinical benefit from radionuclide treatment for bone pain palliation. It is performed at 2–3 hours following the i.v. injection of 20–30 mCi ^{99m}Tc-MDP/HDP.

TABLE 1.1. COMPARISON OF IMAGING MODALITIES FOR THE DETECTION OF BONE METASTASES [1.15]

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 tumour healing	Varies 62-100%[4]	Varies 78-100%[5]	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 tumour healing	Low 44-50%	Numerical specificity values not addressed	Low ($84.32)
CT	Yes	Local/ regional	Lytic, sclerotic, mixed for bone, higher attenuation for marrow	Lysis/sclerosis not at treshold for detection	Trauma, inflammation, benign tumour 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	W hole 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 tomography.

[2] Whole body, the entire body is studied at one time image; regional, large anatomic are studied at one time with one image; and local, focal or small anatomic area studied at one time with one image.

[3] Estimates are based on Medicare fee schedules for Harris County, TX. Low, less than $250; moderate, $250 to $999.99; high, more than $1000 (Values are given in US 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 or MRI may be useful for obtaining whole-body images in a reasonable time, but the cost of central axial skeletal imaging remains high.

1.4.2. Assessment

Patients with bone metastases commonly present with symptoms of pain. A detailed history should be taken, with regard to all symptoms, including pain, difficulty in walking; sleep disturbance etc. Specific questions should be directed to the assessment of pain and should include the location of pain, intensity and its character, breakthrough pain, relation to movement and weight bearing and relieving factors. Multiple sites of pain may occur and each should be separately recorded; the use of body sketch diagrams may aid in this. Associated conditions should also be included in the history for example constipation,

polyuria, thirst or confusion which may herald hypercalcaemia and weakness, sensory or sphincter changes which may warn of early spinal canal or nerve root compression. Pain assessment is most accurate when recorded by the patient; the commonly used self report assessment tools for pain are a numerical rating scale (NRS), visual analogue scale (VAS), and adjective rating scale (ARS). Continuous scales may be from one to ten or one to 100 where zero is no pain and the maximum score (10 or 100) stands for worst pain or intolerable pain. They are most helpful if used at the beginning of treatment and at each follow up visit. Pain assessment should include analgesic use. These are conveniently recorded using the WHO 3 step ladder pattern and converting drug doses into daily oral morphine equivalents. This should include regular doses and breakthrough doses. In addition adjuvant medications should be recorded. Pain should be assessed and documented at regular intervals, before and after starting a treatment plan, Updates for each new report of pain are important using throughout objective diagrams and rating scales. The ABCDE approach to pain management shown in Table 1.2 is recommended.

TABLE 1.2. "ABCDE" FOR PAIN ASSESSMENT AND MANAGEMENT

A	– Ask about pain, and assess pain systematically.
B	– Believe the patient and family in their reportage of pain and how it is relieved.
C	– Choose pain control options appropriate for the patient, their family and the local settings.
D	– Deliver the interventions in a timely logical and coordinated fashion.
E	– Empower the patients and family so as to enable them to control their pain to the greatest extent possible.

Pain assessment should include a thorough physical examination with particular attention to the musculoskeletal and neurological systems. Evaluation of local tenderness, limitation of movement, sensory and motor changes is essential and the cranial nerves, rectal and bladder sphincter function should not be overlooked. Various functional scales are available to give an objective measure of physical capabilities e.g. American Spinal Injury Association scales shown in Table 1.3.

TABLE 1.3. GRADING OF MOTOR FUNCTION (AMERICAN SPINAL INJURY ASSOCIATION)

0	Complete paraplegia
1	Palpable or visible muscle contractions
2	Active movement of the leg without gravity
3	Active movement against gravity
4	Against mild resistance
5	Against moderate resistance
6	Against severe resistance
7	Normal strength

There is no specific Quality of Life (QOL) module available for bone metastases. This is under development for the EORTC QLQ C30. Generic core quality of life scales using the EORTC or FACT scales may be considered but at present they do not have role in routine treatment of bone metastases outside a research setting.

Response may be defined as complete response, partial response, no response or progression, incorporating both pain and analgesic scores as shown in Table 1.4.

TABLE 1.4. RESPONSE DEFINITIONS

Complete response defined as pain score zero at treated site with no concomitant increase in analgesic intake.
Partial response defined as pain reduction of two or more at the treated site on a 0–10 scale without analgesic increase or analgesic reduction of 25% or more from base line without an increase in pain.
Progression / no response defined as increase in the two or more points in 0–10 scale above base line at the treated site with stable analgesic use or increase of 25% or more, with pain score stable or one point above base line.

It may be difficult to focus on a localized pain response when the pain may originate from multiple sites. Assessments should be done at 4 weeks, 8 weeks and 12 weeks. Response to radiotherapy is usually seen in the first 4 to 6 weeks and is unlikely after 8 weeks; at this point alternative treatments should be introduced if the pain persists. Follow up is best undertaken through clinic visits and patient completed questionnaires will give the most accurate measures of response. However where distances are large it can be done by mail or telephone with the help of pre-structured questionnaires. As well as the original site of pain it is important to be alert to new problems of pain and possible complications developing. There is however no role for routine X rays, scans or biochemical markers.

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CHAPTER 2
EXTERNAL BEAM RADIOTHERAPY

2.1. Local pain from uncomplicated metastasis

The analgesic effects of radiation on painful bone metastasis has been recognized for many years with early reports found from the beginning of the twentieth century, not long after the discovery of X rays [2.1]. Local radiotherapy is probably the treatment of choice for localized bone pain. There is now a large body of published literature which confirms the efficacy of this treatment. Overall 70 to 80% of patients will respond and up to a third will achieve a complete response. Definitions of response vary between different studies. The most reliable use prospective patient scores using either a simple four point categorical scale or a 10 mm visual analogue scale. Inclusion of analgesic use and changes in analgesic requirements may also be incorporated into response criteria and complete response refers to patients achieving a state of no pain recorded either with or without analgesia. Formal endpoints for studies in metastatic bone pain trials have now been published in an international consensus statement [2.2].

The treatment technique will depend upon available equipment. Many bones for example the ribs and lumbosacral spine are superficial and can be treated very effectively with orthovoltage (250 to 300 kV) X rays. For deeper seated bones in the cervical and dorsal spine, the long bones, pelvic and shoulder girdle bones then megavoltage energies are necessary. Adequate treatment can be delivered with cobalt although 4 to 6 MV photons from a linear accelerator are perhaps ideal. Most patients will have multiple metastases and therefore the clinical target volume is defined by sites of pain and local tenderness rather than the radiological extent of metastases, unlike the situation in radical treatment. Clinical identification of the bone site responsible for pain and radiological confirmation that this is associated with a bone metastasis and not due to another mechanism, for example osteoporotic collapse or degenerative joint disease is essential.

Planning may involve simple clinical definition of the tender area and clinical set-up on an orthovoltage or cobalt machine using an appropriate applicator or field size. A margin of 2 to 3 cm around the tender bone should be used. Patient positioning may be critical particularly where the patient is in pain. Where an applicator set-up with orthovoltage or electrons is in use then this should be in the most comfortable position for the patient consistent with applicator access to the site. For megavoltage beam treatments then the patient should be prone or supine whichever is most comfortable for them provided under couch treatment can be accurately delivered if the spine is to be treated with the patient supine. No formal immobilisation is usually required but adequate analgesia should be available to the patient during the planning and treatment procedure.

It is recommended that wherever possible an X ray simulator is used; this will provide best localisation for the spine, pelvis and long bones. Similar principles will be adopted with the patient prone or supine as appropriate, defining a field to cover the tender bone with a 2 to 3 cm margin, bearing in mind that the field edge defined by the wires of the simulator will usually reflect the 50% isodose. Other considerations are that when treating the spine field edges should ideally be at intervertebral spaces and the field symmetrical about the midline unless there is a significant paraspinal soft tissue mass. Where there is significant scoliosis then the field may need to be widened and if necessary lead shielding used to ensure full coverage of the vertebrae. In the pelvis it will generally be preferable to treat to the midline and where there is pain in the ileum and sacrum then both sacro-iliac joints are better included than attempting to junction through these areas. It should always be borne in mind that many

of these patients will require re-treatment either to the same site or an adjacent site and therefore issues with regard to possible field matching must be taken into account. With this in mind wherever possible a permanent record of the simulated film should be taken with either an X ray image or digital reconstructed image. Similarly field edges should be marked and because of the importance of field matching, particularly over the spine, permanent tattoos used so that they can be reproduced as necessary should re-treatment be required.

For many situations a single field will be adequate with the dose prescribed as the incident 100% dose either on the surface or at build-up depth for megavoltage beams. For deeper bones, particularly long bones and the pelvis, then anterior and posterior parallel opposed fields will be used with the dose described to the intersection point. Rarely a planned volume may be appropriate for example when there is a large soft tissue mass adjacent to the spine associated with a bone metastasis.

2.1.1. Radiation dose

The optimal radiation dose for the treatment of localized bone metastasis with radiotherapy has been the subject of considerable research activity in the past two decades. Over this time over 3500 patients have been entered into randomized controlled trials comparing hypofractionation, typically a single fraction with multifractionation schedules. These trials have now been subject to three meta-analyses [2.3–2.5] of which the most recent included 12 trials with a total of 3508 patients. This meta-analysis confirmed the results of the two previous meta-analyses and the individual trials themselves by showing no difference in either complete or partial response from treatment between any of the dose fractionation schedules used. The overall response rate was 60% and the complete response rate 33%. The most recent of these studies from the RTOG has finally confirmed that even in a US setting, single dose radiotherapy is effective for metastatic bone pain, counteracting the results of the early RTOG 74-02 study which proposed on the basis of a reanalysis of the data that multifraction treatment was advantageous. The more recent RTOG 97-02 randomized 898 patients to receive either 8 Gy or 30 Gy in 10 fractions. The overall response rate was 66%. Complete and partial response rates were 15% and 50%, respectively, in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm [2.6].

There is therefore overwhelming clinical trial evidence to show that a single dose of 8 Gy is adequate and for palliation optimal for the patient with localized metastatic bone pain. There is no role for multifraction treatment in uncomplicated bone metastasis.

This trial data confirms the many case report series which preceded it using single doses ranging between 4 and 10 Gy, a selection of which are shown in Table 2.1 [2.7].

TABLE 2.1. SINGLE-FRACTION SINGLE-ARM STUDIES [2.8–2.17]

Author	Year	RT dose	Overall response rate
Vargha, Z.O., et al.	1969	4–18 Gy	90%
Penn, C.R.M.	1976	8–15 Gy	89%
Hendrickson, F.R., et al.	1976	9 Gy	88%

Author	Year	RT dose	Overall response rate
Jensen, N.H., Roesdahl, K.	1976	3–7.5 Gy	85%
Quasim, M.M.	1977	8–10 Gy	82.5–85%
Ambrad, A.J.	1978	15 Gy	100%
Barak, F., et al.	1987	6–10 Gy	71%
Price, P., et al.	1988	4 Gy	48%
Karstens, J.H., et al.	1989	4 Gy	45%
Uppelschoten, J.M., et al.	1995	6 Gy	88%

Overall response rates comparable to those found in the randomized trials of around 80% are seen, with the exception of the two lower dose 4 Gy studies. Whilst lower doses than 8 Gy are also effective for metastatic bone pain, their relative efficacy has been studied prospectively demonstrating a dose response for bone pain relief emerging at this point. Two studies have looked at doses of 6 Gy and 4 Gy [2.18–2.19]. Whilst statistically less effective both doses achieve pain relief in a significant number of patients with a response after 4 Gy of around 45%. Such lower doses can therefore be considered, particularly where re-treatment is to be considered over the spinal cord if there is concern with regard to radiation tolerance.

The efficacy of such low doses presents interesting hypotheses with regard to the mechanisms of pain relief after radiotherapy. Increasingly it appears that tumour cell kill may not be fundamental to the process although on the basis of cell culture data measuring surviving fraction of cells after 2 Gy a significant amount of cell kill is seen with initial exposure to radiation, the SF2 for non small cell lung cancer being 0.89 and for breast cancer being 0.88 and the respective values for surviving fraction after 8 Gy being 0.17 and 0.13 [2.20–2.21]. It is increasingly clear from a knowledge of the pathophysiology of bone pain that complex biochemical processes involving osteoclast activation and multiple neurotransmitter pathways through the large C fibres are responsible for the pain of bone metastases. Indirect evidence based on measurement of urinary markers of bone turnover suggests that radiotherapy to a painful bone metastasis will reduce the excretion of such markers, strongly supporting the hypothesis that the osteoclast may be an important target for radiotherapy in producing its analgesic effect [2.22]. Furthermore the degree of osteoclast marker suppression has been shown to predict for response to radiotherapy for bone pain.

One feature which has been identified in patients receiving single dose radiotherapy for metastatic bone pain is that a larger proportion will have re-treatment. The actual reason for re-treatment is often not clear in the controlled trials and there is clearly an element of both patient and physician choice and bias. The rates of re-treatment in recent trials of fractionation regimes in metastatic bone pain in shown in Table 2.2 [2.23]:

TABLE 2.2. PROSPECTIVE RANDOMIZED TRIALS EVALUATING VARIOUS SINGLE & FRACTIONATION REGIMENS [2.6, 2.18, 2.19, 2.24–2.27, 2.99]

Study	Retreatment rate	
	Low dose arm	High dose arm
(i) Single dose 8 Gy vs multifraction		
UK Bone Pain Trial	11%	3%
UK Bone Pain Trial	23%	10%
Dutch Bone Pain Trial	25%	7%
Danish Bone Pain Trial	20%	12%
RTOG 97-02	18%	9%
TROG 9605	29%	24%
(ii) Single dose 8 Gy vs 4 Gy		
Jeremic et al	42%	38%
UK 8 Gy vs 4 Gy	20%	9%

It can be seen that overall around 25% of patients are re-treated after a single dose of radiation. Re-treatment is both feasible and effective after single doses of 8 Gy even over the spinal cord and a further single dose of 8 Gy or a fractionated schedule of 20 Gy in 5 fractions is perfectly safe. There is no recorded incidence of myelitis after such practice. Response after re-treatment is similar to that with primary treatment. A retrospective analysis of 105 consecutive patients in whom 280 individual retreatment sites were identified reported an overall response rate for retreatment of 87% [2.28]. Furthermore in this series a small number of patients received a second retreatments in whom 7 out of 8 (88%) patients achieved pain relief The use of a single fraction of 4 Gy has been shown to be effective also [2.28]. In a series of 135 patients of whom 109 were re-treated because of pain relapsing and 26 were re-irradiated after initial non-response the response rate was 74% for pain relapse and 46% in non responding patients after initial treatment [2.29]. In a further series of patients having pain after two single dose treatments, a further single 4 Gy re-irradiation resulted in an overall response rate of 80%, with both complete response and partial response being 40% [2.30]. Thus it is important to consider reirradiation even in patients who fail to respond well initially and even in those who may relapse or fail to respond after two treatments.

An analysis of re-treatments in a large Dutch bone pain trial suggests that there is a higher response rate after single doses of 8 Gy, which was 66% in this study, than after fractionated schedules and that re-treatments are more effective in breast cancer patients than prostate cancer patients [2.31]. However, when considered overall, even allowing for re-treatment in the comparison between single and multifraction radiotherapy this trial continued to show no advantage for the multifraction treatment.

Re-treatment with a single dose of 8 Gy therefore is feasible, safe and effective. This should be considered in all patients who have persistent or recurrent bone pain.

The timing of re-treatment should be reflected against the known pattern of response to local radiotherapy. There is a consistent pattern seen in which there is an ever-increasing incidence of response within a treated population which reaches a plateau at 4 to 6 weeks after treatment. Patients should therefore be encouraged to wait 4 weeks at least after treatment before considering re-treatment during which time there is a continuing probability of response from the first radiation exposure.

2.1.2. Toxicity

In general local radiotherapy for metastatic bone pain is well tolerated. Acute toxicity is mild and self-limiting after doses of 8 Gy or the more prolonged fractionated schedules. In the most recent RTOG trial 97-02 there was an excess of acute Grade 2–4 toxicity in the multifraction 30 Gy arm compared to the single dose 8 Gy arm (17% vs 10% p=0.002). Up to one third of patients will experience some degree of nausea and anorexia particularly where large volumes encompassing the pelvis and thoraco-lumbar spine are treated. Such patients should be offered prophylactic anti-emetics. The actual drugs used will depend upon availability. The most effective schedules are probably combinations of dexamethasone with a 5HT3 antagonist for example dexamethasone 8mg with granisetron 2mg which can be taken orally half an hour before radiotherapy and continued for 24 to 48 hours after treatment. Alternative schedules using more readily available drugs such as metoclopramide or cyclizine are equally acceptable.

Treating the pelvis may result in short-lived diarrhoea but many patients are on large doses of analgesics also which will mitigate against this.

Other radiation reactions are not usually seen. Pain flare may be seen after local radiotherapy for bone pain and has been reported in up to 14% of patients on the day after radiotherapy [2.32]. Appropriate additional analgesia should be available to the patient to cover this possibility.

2.2. Multi-site pain from uncomplicated metastasis

Bone metastasis are typically multiple and a common clinical picture is that of pain in several different sites often flitting from one site to another. Local radiotherapy in this setting is generally unsatisfactory resulting in patients requiring multiple treatment visits to have different sites treated. In this setting therefore external beam radiotherapy should be given as wide field radiotherapy or hemibody radiotherapy.

Conventionally hemibody radiotherapy is considered as upper hemibody (UHBI) or lower hemibody (LHBI) the midpoint being defined at the umbilicus. In practice in the management of bone metastasis this is often not a useful designation and it is better to consider this treatment in terms of wide field radiotherapy using large external beam fields to cover the painful sites whether above or below the umbilicus. Thus for example pain in the thoraco-lumbar spine and pelvis can be included in a single field which would effectively be the mid-hemibody.

Wide field radiotherapy requires megavoltage beam treatment. Cobalt beams are adequate although may require a high entry dose at the treatment portal to achieve the midplane dose. Six MV photon beams are preferable. Painful sites should be identified clinically and the

presence of underlying bone metastasis confirmed. The treatment field can be set up clinically or preferably with an X ray treatment simulator. A typical modern linear accelerator will be able to achieve a field size of up to 40cm × 40cm at 100cm SSD. Extended FSD techniques can be used to achieve larger fields than those possible at standard FSD operation. Appropriate corrections to output factors and dosimetry will then be required. The patient will typically be supine on the treatment couch but if this causes considerable discomfort a prone position is possible. Complex dosimetry is not required for such treatments. The prescription dose is typically prescribed to the midplane at the field centre. Compensation for changes in contour is not usually needed.

The critical organ at risk limiting dose in this setting is the lung. Lung tolerance at linear accelerator dose rate, approximately 1 Gy per minute, is 6 Gy [2.33]. Above this dose a significant incidence of acute pneumonitis will be seen which is usually fatal. This should therefore be regarded as an absolute maximum dose whenever lung is included in the hemibody or wide field treatment volume. Thus treatments encompassing the upper hemibody will receive 6 Gy midplane dose and those encompassing the lower hemibody 8 Gy midplane dose. Other schedules have been described for example 8 Gy in 2 fractions over two days with similar results [2.34] but there is no clear advantage for fractionated treatment in this setting and a single dose is practical, safe and effective.

Wide field radiotherapy is inevitably associated with greater toxicity than local radiotherapy. The commonly encountered toxicities are gastrointestinal and bone marrow. Overall upper hemibody treatments may be associated with up to 16% of moderate or severe toxicities and lower hemibody treatments up to 9% [2.34]. For this reason prophylactic treatment is recommended particularly for acute gastrointestinal toxicity. The optimal treatment has yet to be defined. In the past intensive schedules requiring inpatient care with active hydration intravenously, sedation, steroids and anti-emetics was recommended. The use of modern 5HT3 antagonists has largely superseded the need for such intensive measures. For the majority of patients pre-treatment with dexamethasone 8 mg and granisetron 2 mg or an equivalent 5HT3 antagonist given half an hour before treatment exposure will be adequate and prevent most serious side effects. Continuing the anti-emetic schedule for 48 hours is recommended. Patients should have access to anti-diarrhoeal medication although many will already be on significant doses of opioid to address this.

Pain flare is seen in less than 10% of patients for which supplementary analgesia should be made available.

Bone marrow depression is rarely clinically relevant except in patients who already have severely compromised bone marrow function in whom there are relative contra-indications to this treatment. Patients starting with a normal full blood count, that is haemoglobin > 10 g/dl, white count $>3.0 \times 10^9$/l, neutrophils $>1.5 \times 10^9$/l, platelets $>100 \times 10^9$/l, should not encounter clinically relevant toxicity and do not require active monitoring. Patients who have wide field radiotherapy who have impaired bone marrow function and blood counts which do not fulfill these criteria may require more careful monitoring and even support with blood or platelet transfusion. When falls in count are seen this typically follows a time course over 4 to 6 weeks by which time there is complete recovery.

Hemibody radiotherapy is highly effective for pain relief. A similar number of patients will achieve response as after local radiotherapy, that is around 70% of patients will have at least a partial reduction in their pain. One striking feature of wide field radiotherapy is that responses

are often rapid with 25% of patients achieving pain relief within the first 24 hours after treatment [2.35–2.36].

2.3. Metastatic spinal cord compression (MSCC)

Metastatic spinal cord compression (MSCC) is defined as "Comprehensive indentation, displacement, or encasement of the thecal sac that surrounds spinal cord or cauda equina by spinal epidural metastases". It may be caused either by posterior extension of a vertebral body mass (most common), by anterior extension of a mass arising from the dorsal elements, or by growth of a mass invading the vertebral foramen (least common). The thoracic spine as the longest part is more involved than the other parts, cervical spine < 10%, thoracic spine 60–80%, lumbar spine 15–30%.

MSCC occurs in 5–10% of all cancer patients during the course of their disease [2.37]. The incidence depends on the type of primary tumour and ranges from 0.2% in pancreatic cancer to 7.9% in myeloma [2.37]. The most common primary tumours in MSCC patients are breast cancer, prostate cancer and lung cancer, each accounting for about 20% of the patients, and myeloma [2.38]. MSCC may be associated with various neurologic signs such as pain, motor deficits, sensory deficits, and autonomic dysfunction (Table 2.3). If pain is the only clinical symptom or if the diagnosis is based on radiologic studies alone, it should be described as "impending MSCC". The treatment of pain is described in the preceding chapters.

TABLE 2.3. CLINICAL SYMPTOMS OF MSCC [2.39–2.42]

Reference	Patients N	Pain (%)	Motor deficits (%)	Sensory deficits (%)	Autonomic dysfunction (%)
Bach, *Acta Neurochir*, 1990	398	83	67	90	48
Helweg-Larsen, *IJROBP*, 2000	153	88	61	78	40
Gilbert, *Ann Neurol*, 1978	130	96	76	51	57
Kovner, *J Neurooncol*, 1999	79	70	91	46	44

In case of neurologic deficits due to MSCC such as motor dysfunction, urgent treatment is required in order to avoid progression especially of motor deficits that may result in paraplegia [2.43]. Radiotherapy (RT) and decompressive surgery are the most important treatment modalities [2.44].

Because the indication for surgery of MSCC is usually limited to patients with a good performance status, a survival prognosis of more than 3 months, and involvement of only one spinal segment, which account for only about 10% of all MSCC patients, radiotherapy alone still is an important modality for MSCC [2.44].

Irradiation is performed either with 6–16 MV accelerators or with cobalt 60 units. The radiation technique depends on the location of MSCC and on the distance from the patient's

surface (skin) to the spinal cord. MSCC of the cervical spinal cord should be treated with two lateral opposed fields to keep the dose in the oral cavity as low as possible and to avoid dose inhomogeneity caused by the shoulders. Radiation of MSCC in the thoracic and lumbar spinal cord is performed either with a single posterior field or with two anterior-posterior opposed fields. The radiation techniques and the energies in relation to the depth dose distribution is shown in Figure 2.1. The curves represent a single posterior field with 6 MV photons, two anterior-posterior fields with 16 MV photons (anterior fields) and 6 MV photons (posterior field), and two anterior-posterior fields with 16 MV photons for both fields. To avoid a maximum dose in the spinal cord of more than 115%, a single field technique is recommended if the distance between skin and posterior part of the vertebral body is 5 cm or less. If it is more than 5 cm, a technique with two opposed fields is more appropriate.

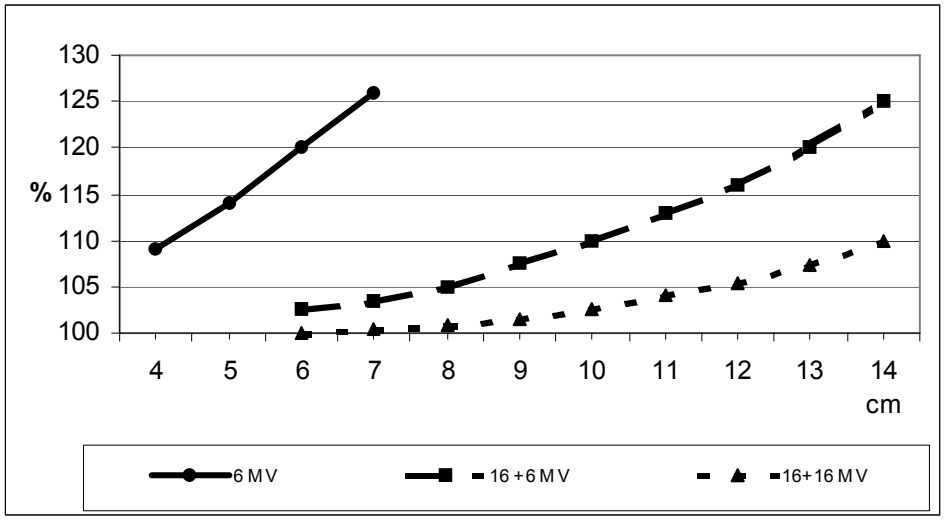

FIG. 2.1. Depth-dose distribution of various radiation techniques and energies.

Regarding the anatomy, the most important area is the posterior part of the vertebral body, from where the metastasis compresses or infiltrates the spinal cord. Thus, the radiation doses should be prescribed to the posterior border of the vertebral body, which can easily be defined by computed tomography or magnetic resonance imaging. If such imaging facilities are not available, radiation doses can be approximately defined (depending on the patient's nutritional status) to a depth of 5–6 cm in the thoracic spinal cord and 6–8 cm in the lumbar spinal cord. The treatment volume should encompass one or two normal vertebrae above and below the metastatic lesions.

Radiotherapy must be supplemented by administration of dexamethasone, which should be started as soon as possible, usually before the first radiation fraction can be delivered. However, the appropriate dose of dexamethasone is still a matter of debate. High-dose dexamethasone (96–100 mg/day) appeared more effective than low-dose dexamethasone (10–16 mg/day), but was associated with significantly more serious adverse effects (Table 2.4). Moderate-dose dexamethasone (16–32 mg/day) is administered and proven to be effective and safe.

TABLE 2.4. ADMINISTRATION OF DEXAMETHASONE [2.45–2.47]

Reference	Patients N	Study-Design	Dexamethasone doses	Results	Serious adverse effects
Sørensen, *Eur J Cancer*, 1994	57	randomized	96 mg/4 days vs. no steroids	Ambulatory 81% vs. 63% (P=0.046)	11% vs. 0% (psychoses, ulcers)
Vecht, *Neurology*, 1989	37	randomized	100 mg + 16 mg/d vs. 10 mg + 16 mg/d	Improvement 25% vs. 8% (P=0.22)	Not stated
Heimdal, *J Neurooncol*, 1992	66	Case-control study	96 mg/4 days vs. 10 mg + 16 mg/d	Not stated	14% vs. 0% (ulcers, bleeding, perforation)

Many different radiation schedules are used world wide. The most appropriate schedule is still debated. Several prognostic factors have been demonstrated to predict functional outcome after radiotherapy [2.38]. Improvement of motor function was significantly associated with a favorable histology of the primary tumour (e.g. myeloma, lymphoma), with a longer interval (more than 24 months) between tumour diagnosis and MSCC, with involvement of only 1–2 vertebrae, with a slower development (more than 14 days) of motor deficits before radiotherapy, with being ambulatory before radiotherapy, and with a good performance status.

One has to be aware, that MSCC represents a palliative situation. Median survival of MSCC patients usually ranges between two and six months (Table 2.5).

TABLE 2.5. MEDIAN SURVIVAL OF MSCC PATIENTS [2.48–2.56]

Author	Year of publication	N patients	Median survival time after RT (months)
Sorensen, P.S., et al.	1990	149	2.3
Kim, R.Y., et al.	1990	59	2.5
Maranzano, E., et al.	1995	209	6
Helweg-Larsen, S., et al.	1995	107	3.4
Maranzano, E., et al.	1997	53	5
Rades, D., et al.	1999	96	4
Rades, D., et al.	2001	131	5
Hoskin, P.J., et al.	2003	102	3.5
Maranzano, E., et al.	2005	276	4

Transport to the radiotherapy department and the positioning on the treatment couch, every treatment session may cause major discomfort to the often debilitated patients. A schedule with a short overall treatment time (short-course radiotherapy) appears preferable, especially for patients with a markedly reduced life expectancy, as it is more patient convenient and less time consuming. Short-course radiotherapy regimens such as 1 × 8 Gy and 5 × 4 Gy (overall

treatment time ≤1 week) can be recommended, if they provide similar outcome as more protracted schedules such as 10 × 3 Gy, 15 × 2.5 Gy, and 20 × 2 Gy (long-course radiotherapy). Several authors compared different fractionation schedules for their impact on motor function in MSCC patients [2.38, 2.55–2.58]. All of these studies demonstrated short-course radiotherapy and long-course radiotherapy to be similarly effective for functional outcome (Table 2.6).

Life expectancy of MSCC patients varies between different primary tumours [2.50, 2.55, 2.59]. Breast cancer patients, prostate cancer patients, and myeloma patients developing MSCC may live for several years after radiotherapy. Furthermore, different tumours show a great variation regarding radiosensitivity [2.59]. Thus, it appears reasonable to consider each tumour entity a separate group of MSCC patients. Since 2005, several analyses on functional outcome after radiotherapy of MSCC patients have been available that compare short-course and long-course radiotherapy and focus on single tumour entities such as breast cancer, prostate cancer, non-small cell lung cancer, myeloma, and renal cell carcinoma (Table 2.7). Both short-course and long-course radiotherapy resulted in comparable functional outcome in breast cancer, prostate cancer, lung cancer, and renal cell carcinoma patients [2.60–2.63]. In myeloma patients, long-course radiotherapy appeared to be associated with significantly better functional outcome than short-course radiotherapy at 6 months (67% versus 43% improvement of motor function, P=0.043) and at 12 months (76% versus 40%, P=0.003) and therefore appeared to be more effective [2.64]. A trend was observed at 1 month (59% versus 39%, P=0.10) following radiotherapy. The retrospective nature of the analysis should be taken into account when interpreting the data.

TABLE 2.6. COMPARISON OF DIFFERENT FRACTIONATION SCHEDULES FOR FUNCTIONAL OUTCOME [2.38, 2.55–2.58]

Reference	Patients N	Study-Design	Schedules	Results
Hoskin, Radiother Oncol, 2003	102	retrospective	1–2 fractions vs. multifraction	similar functional outcome
Rades, Cancer, 2004	214	prospective	10 × 3 Gy vs. 20 × 2 Gy	similar functional outcome
Rades, IJROBP, 2005	204	retrospective	1 × 8 Gy vs. 10 × 3 Gy	similar functional outcome
Maranzano, J Clin Oncol, 2005	276	randomized	2 × 8 Gy vs. 3 × 5 Gy + 5 × 3 Gy	similar functional outcome
Rades, J Clin Oncol, 2005	1304	retrospective	1 × 8 Gy vs. 5 × 4 Gy vs. 10 × 3 Gy vs. 15 × 2.5 Gy vs. 20 × 2 Gy	similar functional outcome

TABLE 2.7. FUNCTIONAL OUTCOME AT 1 MONTH FOLLOWING RADIOTHERAPY RELATED TO DIFFERENT PRIMARY TUMOURS [2.60–2.64]

	Improvement N (%)	No change N (%)	Deterioration N (%)	P
Breast cancer (N=335)				
Short-course radiotherapy	44 (34)	74 (57)	12 (9)	
Long-course radiotherapy	61 (30)	118 (58)	26 (12)	0.81
Prostate cancer (N=281)				
Short-course radiotherapy	52 (34)	78 (50)	25 (16)	
Long-course radiotherapy	40 (32)	72 (57)	14 (11)	0.83
Non-small-cell lung cancer (N=252)				
Short-course radiotherapy	16 (15)	58 (55)	31 (30)	
Long-course radiotherapy	19 (13)	78 (53)	50 (34)	0.87
Myeloma (N=172)				
Short-course radiotherapy	24 (39)	35 (58)	2 (3)	
Long-course radiotherapy	66 (59)	43 (39)	2 (2)	0.10
Renal cell carcinoma (N=87)				
Short-course radiotherapy	10 (27)	24 (65)	3 (8)	
Long-course radiotherapy	15 (30)	28 (56)	7 (14)	0.91

In addition to functional outcome, local control of MSCC following radiotherapy is another important endpoint. Local control of MSCC is defined as absence of a recurrence of MSCC associated with neurologic symptoms deficits in the previously irradiated area of the spinal cord (‘in-field recurrence’). It has been demonstrated that short-course radiotherapy is associated with significantly more in-field recurrences than short-course radiotherapy (18% versus 5% at 1 year, P<0.001) [2.38]. Again, the retrospective nature of that analysis has to be considered. MSCC patients with a relatively good survival prognosis may live long enough to develop an in-field recurrence of MSCC. Because survival of MSCC patients varies considerably between the different primary tumours, separate analyses of single tumour entities for local control of MSCC are important. In the patients of our analyses that focused on five different types of primary tumour (see above), long-course radiotherapy was associated with significantly better 1–year local control rates than short-course radiotherapy in breast cancer patients (96% versus 84%, P=0.008) and prostate cancer patients (94% versus 77%, P=0.001). The results for non-small cell lung cancer, myeloma, and renal cell carcinoma patients were not significant.

If an in-field recurrence of MSCC occurs after short-course radiotherapy, spinal re-irradiation with 1 × 8 Gy, 5 × 3 Gy, or 5 × 4 Gy can be safely performed [2.65]. In a series of 62 patients, 40% showed improvement of motor function after re-irradiation, and 38% of the previously non-ambulatory patients regained the ability to walk. Radiation myelopathy was not observed after a median follow up of 12 months (range 4–42 months) following re-irradiation.

In summary, Iong-course radiotherapy appears preferable for breast cancer and prostate cancer patients with a good survival prognosis, because it is associated with fewer MSCC recurrences in patients with such tumours.

In myeloma patients, functional outcome appeared better after long-course radiotherapy suggesting long-course radiotherapy to be more effective for this entity. However, these results need to be prospectively confirmed.
Breast cancer and prostate cancer patients with a poor estimated survival may be treated with short-course radiotherapy, because they may not live long enough to develop a recurrence,

and short-course radiotherapy means more patient-convenience. MSCC patients with non-small-cell lung cancer, renal cell carcinoma, and other types of carcinoma should be considered for short-course radiotherapy.

2.4. Pathological fracture

Progressive involvement of the bone cortex weakens the axial strength of the bone and gives rise to instability. Fracturing of lesions most often occurs in the upper and lower extremities or in the vertebrae of the spine, with sometimes no or only small injury provoking the event. Even in bed-ridden patients long bones tend to fracture due to torsional forces when patients turn in their beds [2.66]. It is a very painful traumatic event for the patient and often requires immediate stabilization and immobilisation to treat the pain and to prevent further complications. The choice of the most appropriate treatment for impending or actual fractures of the bone depends on the operability of the patient and his life expectancy. To minimize the chance of a pathological fracture in weight-bearing bones it is important to search for lesions at risk of fracturing and treat them aggressively. Unfortunately, it is difficult to predict which lesions are at risk using radiographic imaging and clinical information. Current indications for prophylactic treatment come mostly from retrospective studies and have not been clearly defined [2.67, 2.68]. Prediction of fracturing based on lesional characteristics is therefore considered to be not very accurate and needs further refining [2.69, 2.70].

2.4.1. Impending fractures of the femur / humerus

The occurrence of a pathological fracture in a metastatic lesion in the femur or humerus causes the patient considerable morbidity. Therefore, prevention of fractures is an important palliative treatment to stabilize the bone and to assure functions like walking. Metastatic lesions with a high risk of fracturing require elective surgical stabilization using prophylactic osteosynthesis, such as intramedullary nailing, plate and screws, or, for proximal femoral lesion, total hip replacement. An advantage of elective surgery is that patients with a relatively good performance are easier to operate on with less morbidity and mortality than after pathological fracture has occurred. Painful low risk lesions, however, can be treated conservatively using less invasive treatment modalities like external beam radiotherapy, chemotherapy, hormonal therapy or regular infusions with bisphosphonates to induce remineralization of the affected bone [2.71–2.76]. However, the strengthening effect of these non invasive treatments will take weeks to months.

Physicians often rely on their subjective intuitive sense, because it is difficult to differentiate between low risk and high risk lesions based on the available radiological information. Several authors have tried to formulate objective risk factors for impending fracturing of extremities, using mostly surgical and retrospective data, in order to decide which lesions need prophylactic osteosynthesis and which can be treated conservatively (Table 2.8) [2.68]. Frequently mentioned are the size of a lesion (> 25 mm), proximally located lesions [2.77–2.82], a radiographic osteolytic appearance [2.66, 2.77–2.79, 2.81–2.85], the percentage of circumferential or axial cortical involvement > 50% [2.67, 2.69, 2.79, 2.82, 2.84, 2.86–2.91], and increasing local pain [2.69, 2.77–2.79, 2.82–2.86, 2.90, 2.92, 2.93]. In 1989, Mirels proposed a scoring system for fracture prediction in which several radiographic and clinical factors were combined into a single score [2.82].

TABLE 2.8. CONVENTIONAL RISK FACTORS FOR IMPENDING FRACTURING OF METASTATIC LESIONS IN THE FEMUR: REVIEW OF THE LITERATURE

	Publication year	Number of femoral lesions[a]	Increasing pain	Lesion size	Radiographic osteolytic appearance	Proximal lesion	Ratio width metastasis / bone	Transverse	Axial	cortical destruction	Circumferential	cortical destruction	Primary tumour	Remarks
Snell [2.77]	1964	19 (19)	+	> 25 mm	+			+	+		+			At risk: any lesion > 25 mm invading cortex
Parrish [2.86]	1970	103 (99)	+								> 50%			Advancing cortical destruction
Beals [2.78]	1971	34 (3)	+	> 25 mm	+			+						Five lesions pinned prophylactically
Fidler [2.87]	1973	18(18)	-								> 50%			95% of fractured lesions had cortical involvement > 50%
Zickel [2.83]	1976	46 (34)	+		+			+	+		+		+	Even small involvement of cortex, at risk: lung carcinoma
Cheng [2.80]	1980	75 (4)		-		+					-			At risk: diffusely mottled lesions, 6 lesions fractured before RT[b]
Fidler [2.88]	1981	87 (32)									> 50%			Cort. involv. estimated or measured by using rolled paper tube
Miller [2.81]	1984	136 (14)		> 20 mm	+	+					+			Mentions increased body weight and activity as risk factors
Bunting [2.85]	1985	? (1)			+									Number of femoral lesions studied not noted
Keene [2.91]	1986	516 (26)	-	-	-				+					57% unmeasurable permeative lesions, axial cort. involv. in proximal lesions larger in 11 fractured lesions ($P< 0.01$)
Menck [2.89]	1988	69 (69)					> 0.6		>30 mm		> 50%			If lesions in femoral neck: > 13 mm axial cortical involvement
Mirels [2.82]	1989	78 (27)	+		+	+					> 66%			Scoring system, incl. upper limb lesions, number not mentioned
Yazawa [2.84]	1990	68 (41)	+		+						> 50%			All patients treated surgically: impending and actual fractures
Dijkstra [2.90]	1997	54 (24)	+				> 0.9		>38 mm					Accurate measurements in 50% of the lesions studied
Van der Linden [2.67]	2004	102 (14)	-	-	-	-	-	-	>30 mm		+/-		-	Prospective patient data from randomized trial

[a] Number of actual fractures between brackets
[b] RT= radiotherapy

However, the majority of the patients in these studies presented with a fracture or underwent prophylactic osteosynthesis. Little is known about the natural behavior of similar lesions without surgical fixation. Consequently, it was shown that strict application of these risk factors leads to surgical overtreatment in patients who only have a limited life expectancy [2.68]. Although the circumferential cortical involvement was mentioned by most studies as a risk factor, it is difficult to measure objectively on plain radiographs. It has been proposed that valid objective measurements can only be made with CT scans [2.93]. However, routine use of CT scans for every single bone metastasis is difficult to implement in every day practice. Most authors did not specifically state how they measured the circumferential cortical involvement [2.80, 2.81, 2.83, 2.86, 2.87].

The only study in which patients were prospectively followed after palliative radiotherapy without elective fixation were those in the Dutch Bone Metastasis Study [2.67]. For femoral lesions, the extent of the axial cortical destruction, measured on a diagnostic radiograph, was shown to significantly predict risk fracturing (Figure 2.2). An axial cortical involvement of 30 mm or more will give a 25% chance of fracturing. If this is the case, then these patients ought to be prophylactically operated on, or, irradiated to a higher total dose to induce remineralisation and thus strengthen the bone (e.g. 24 Gy /6 fr., or 30 Gy /10 fr.) [2.71]. Other known risk factors proved to have only limited discriminating power in this study (Table 2.9). Although the use of the axial cortical involvement still leads to surgical overtreatment, its use instead of other conventional risk factors reduces the number of patients referred for unnecessary prophylactic osteosynthesis. Further research is still necessary to more accurately predict the risk of pathological fracturing of the extremities.

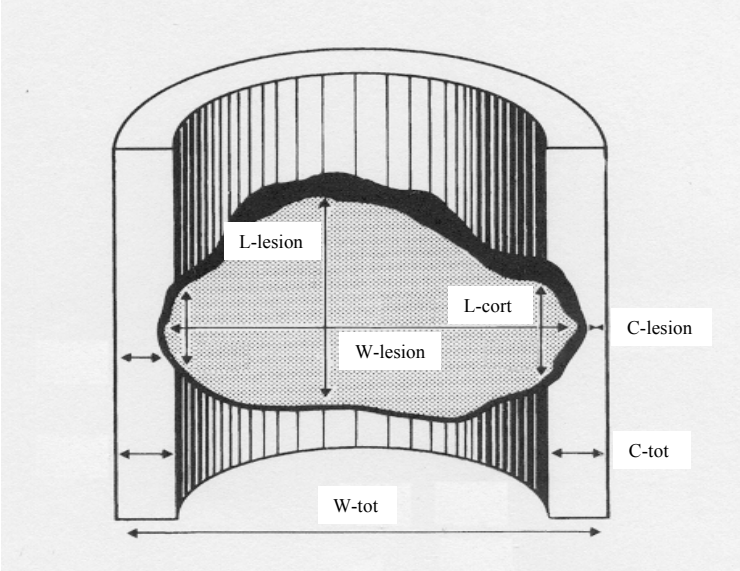

FIG. 2.2. Measurements of metastatic lesions in the femur.

Measurements of metastatic lesions in the femur (in mm): largest axial length of the entire lesion (*L-lesion*), largest transverse extension of the lesion (*W-lesion*), largest axial cortical involvement (*L-cort*). Measurements of the femur (in mm): largest transverse width of the bone (*W-tot*), maximal thickness of cortex without lesional involvement (*C-tot*) and maximal thickness of cortex with lesional involvement (*C-lesion*).

TABLE 2.9. SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES OF RISK FACTORS FOR IMPENDING FRACTURING IN FEMORAL METASTASES IN PATIENTS TREATED WITHIN THE DUTCH BONE METASTASIS STUDY [2.67, 2.82]

	Fracture no (N= 96)	Fracture yes (N= 14)	*P-value*[a]	SE[b]	SP[b]	PPV[c]	NPV[c]
Axial cortical involvement							
≤ 30 mm	56	2	*0.01*	86%	58%	23%	97%
> 30 mm	40	12					
Circumferential cortical involvement							
≤ 50%	79	8	*0.03*	43%	82%	26%	91%
> 50%	17	6					
Scoring system of Mirels[d]							
score 6–8	12	0	*0.36*	100%	13%	14%	100%
score 9–12	84	14					

[a] UV= univariate analysis, using a Cox proportional hazards model
[b] SE= sensitivity, SP= specificity
[c] PPV= positive predictive value, NPV= negative predictive value
[d] To differentiate between high risk and low risk lesions a cut-off point between 8 and 9 was chosen as proposed by Mirels. In: Mirels H. Metastatic disease in long bones. Clinical Orthopaedics and Related Research 249 (1989); 256–264

2.4.2. Actual fractures of the femur and humerus

Pathological fractures in long bones require stabilizing osteosynthesis to restore mobility of the patient and to treat their pain [2.69]. For the upper extremity, fixation with plate and screws or intra-medullary nailing is indicated. For femoral neck fractures a total hip replacement, or gamma nail will be applied, for lower fractures in the intertrochanteric region or shaft, fixation with plate and screws, or intramedullary nail is used.

Radiotherapy is usually administered afterwards to induce remineralization of the fractured bone and stabilize the osteosynthetic prosthesis (e.g. 24 Gy /6 fr., or 30 Gy /10 fr.) [2.71, 2.94]. If the patient is inoperable because of co-morbidity, deteriorating condition, or because the fracture is too complicated, then palliative radiotherapy may reduce pain and enable healing in a considerable percentage of the patients (e.g. 1–2 × 8 Gy, or 5 × 4 Gy).

2.4.3. Vertebral body lesions

(see also Section 2.3 on metastatic spinal cord compression)

For spinal lesions, with or without impending or actual fracture, the choice of palliative treatment depends on the presence and the severity of clinical symptoms, for which the classification of Harrington can be used (Table 2.10) [2.95]. Harrington divided patients into 5 classes depending on the extent of neurological compromise or bone destruction. Primary radiotherapy was recommended for Classes I–III, and primary surgical intervention for Classes IV and V. Harrington noted that secondary surgery should be considered in patients

with pain or neurological symptoms that were refractory to radiotherapy, or when spinal cord tolerance to radiation had been reached [2.95, 2.96]. Several surgical techniques have been developed, ranging from minimal invasive methods, such as palliative decompression by laminectomy, to more extensive procedures, such as radical en-bloc resection and stabilization. The choice of 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 [2.95]. However, it should be noted that many patients with vertebral collapse or instability, even if they are associated with severe local compromise, do not have a sufficient projected life expectancy to warrant such major operative interventions. Adequate prediction of survival, therefore, is crucial [2.97, 2.98].

In general, the choice between surgery alone, surgery plus radiotherapy, or radiotherapy alone depends on the clinical condition of the patient, the time in which the motor and sensory deficits have developed, and the availability of experienced neurosurgeons.

TABLE 2.10. HARRINGTON'S CLASSIFICATION OF METASTASES TO THE SPINAL COLUMN [2.96]

Class I	no significant neurological involvement
Class II	involvement of bone without collapse or instability
Class III	major neurological impairment (sensory or motor) without significant involvement of bone
Class IV	vertebral collapse with pain due to mechanical causes or instability but without significant neurological compromise
Class V	vertebral collapse with pain due to mechanical causes or instability combined with major neurological impairment.

2.5. Neuropathic pain

Neuropathic pain has certain specific features which distinguish it from simple uncomplicated bone pain. It is typically associated with pain or dysaesthesiae which radiates in a distribution of a dermatome often with associated features of altered sensation within that area. The pain is often described as stabbing or burning in nature and may be episodic. The origin of the pain is usually nerve root compression at the exit from the spinal cord, which in the setting of bone metastasis will typically be due to vertebral metastasis. It may also be seen however because of peripheral nerve involvement from rib metastasis affecting the intercostal nerves, long bone metastasis affecting peripheral nerves in the limbs and pelvic metastasis affecting the nerves of the lumbosacral plexus. It is therefore important to identify this pain as distinct from local bone pain and to confirm the site of origin which may be some distance from the actual site of discomfort through a knowledge of the dermatome distribution within the body and likely site of nerve compression. The presence of a metastasis should be confirmed clinically and with imaging. Where available imaging of the peripheral nerve may be helpful with CT or MRI scanning, but this is not essential.

The treatment techniques will be the same as those for local bone pain once the site of origin requiring treatment has been identified (see 2.1 above).

Neuropathic bone pain has been the subject of one randomized controlled trial in radiotherapy comparing dose fractionation schedules of 8 Gy single dose and 20 Gy in 5 fractions. This study randomized 272 patients of whom 89% had spine metastases causing neuropathic pain and 7% chest wall neuropathic pain from rib metastases. Both treatments were highly effective in achieving pain relief which was seen in 53 to 61% of patients with a complete response rate of 26 and 27%. The median overall survival in this study was only 4.8 months with a 1 year survival rate of 27%. Against this the median time to treatment failure of 3.1 months with failure free rate at 1 year of 20% shows that for most patients this treatment was an effective palliation for most of their remaining survival time. Re-irradiation was given to 73 patients out of a total of 160 patients with treatment failure; unlike other bone pain trials where re-treatemnt was more common in the single dose arm the re-treatment rates were 29% for the single dose 8 Gy arm and 24% for the multi-fraction arm.

Overall the single dose arm was not shown to be inferior to the multi-fraction schedule for pain relief and there were no statistically significant differences in the rates of re-treatment, cord compression or pathological fracture. A single dose of 8 Gy should therefore be considered the optimal dose fractionation for neuropathic pain arising secondary to a bone metastasis.

2.6. Cost effectiveness

In the literature, a number of studies have been published concerning the subject of costs versus outcome of different palliative treatments for painful bone metastases.

Four types of cost effect analysis are found in the literature, summarized in Table 2.11.

TABLE 2.11. TYPES OF ECONOMIC EVALUATIONS ANALYSES [2.100]

	Type of analysis	Type of outcome	Question analysed
1	Cost-minimization	Effects are equivalent	What is the least costly treatment?
2	Cost-effectiveness	Clinical effects	What is the most efficient treatment alternative in terms of the defined outcome?
3	Cost-utility	Quality of life effects	
4	Cost-benefit	Financial effects	Which treatment is most efficient if both costs and outcomes are evaluated in monetary terms?

- In cost-minimization analyses (CMA) the effectiveness of the treatments under investigation is considered equal, therefore, the focus lies on the costs. The preferred choice, from an economic point of view, is the treatment with the lowest costs.

- In cost-effectiveness analyses (CEA) the health effect between different treatments is considered. Only one clinical outcome at a time can be addressed, such as life years gained, or local relapse averted in order to make easy comparison possible.

- If more outcomes, such as toxicity or quality of life also are important to study, then, these multiple effects can be combined into one common denominator, such as the quality adjusted life expectancy (QALE), expressed in the amount of quality-adjusted life years (QALY's) gained. This type of analysis is called the cost utility analysis (CUA): it

compares the incremental costs of a treatment to its global health improvement. Utilities range between 0 (=death) and 1(= perfect health).

- Lastly, in cost-benefit analyses (CBA) the clinical effects of treatments are converted into a monetary value. These types of economic analyses are hardly performed in studies on cancer treatments, because it is difficult to translate clinical effects into money.

Important items to be conscious of when interpreting economic analyses are:

- which type of economic analysis is performed,
- is the study on a prospective or retrospective database,
- does it concern true costs and utilities, or, if not, which modelling assumptions have been made,
- are sensitivity analyses and cost effectiveness planes provided, which time frame is considered, etcetera.

In the literature, most analyses that have been performed on the costs and effects of various treatments for bone metastases are cost-minimization or cost-effectiveness analyses, and, most of these focus only on the direct medical costs. In the next section an overview of current literature on this subject will be given.

Literature overview on economic evaluations of radiotherapy for bone metastases

A few studies have calculated **costs only** for different palliative treatments.

(1) Hillner, et al. [2.101] performed a study on the costs of the oral bisphosphonate pamidronate in the prevention of bone complications in metastatic breast cancer. They calculated costs to be US $775 per month.

(2) Ferrel, et al. [2.102] estimated that the costs for oral analgesics taken for cancer pain were US $1000 per patient / month, whereas parenteral use of analgesics mounted to US $4000 per patient / month.

(3) In 1996, a study from the Swedish Council estimated the costs of palliative radiotherapy as approximately US $2000 per patient [2.103].

(4) Glazebrook calculated the costs for radiotherapy in Canada to be C $661 per person per year [2.104].

(5) Macklis, et al. [2.105] performed a cost minimization study on analgesics and radiotherapy. They estimated that the fully allocated costs (direct and indirect) of a course of palliative radiotherapy ranged from US $1200–2500, depending on the number of fractions and the technical complexity of the treatment. Narcotics intake for a 6 month period, i.e. the time frame in which the radiotherapy treatment was considered successful, varied from US $9000–36000.

A few small studies have been performed on **costs, response and survival.**

(1) Stevens, et al. [2.106] found that the costs per month of survival for patients treated with palliative radiotherapy in 1988 was AUS $105.

(2) Rees, et al. [2.107] performed an analysis in which costs, response rate and duration of survival were used as parameters. For palliative radiotherapy, i.e. 10 fractions, response rate 75%, mean response duration 4 months, they calculated the cost per year to be 1200 pounds.

In the literature, five recent larger studies have been published in which **costs and effects** were evaluated.

(1) In 2003, Barton, et al. [2.108] performed a **cost utility analysis** on mostly retrospective data. For the calculation of the utility, duration of survival was used, adjusted for degree of response to pain treatment. For that reason, survival was calculated in a group of 903 patients treated from 1991 to 1996 at the Westmead Hospital in New South Wales, and degree of response was distilled from a literature review of published trials on bone metastases. Average survival was 14.6 months, and adjusted average response was 59%, therefore, the average utility was 14.6 × 0.59= 8.5 months. For costs, they took the 1991 costs of delivering a radiotherapy treatment which was calculated by Smith, et al. [2.109]. Average costs per patient were AUS $855 (i.e. 10.9 treatment fields × cost per field AUS $78). Utility-adjusted costs were AUS $100 / month (i.e. total costs AUS $855 / total number of utility-adjusted months of response 8.5). In addition, a sensitivity analysis in which the response rates from the literature were varied and hence the costs showed a range of costs from AUS $80 to 139.

(2) In 2004, Konski developed a **Markov model** to evaluate the effectiveness of different palliative treatments for painful bone metastases [2.110]. He constructed a reference case: a man with hormone refractory prostate cancer. In the model, patients spent 1 month in each transition state, which differed for each treatment. The end of the model was reached at 24 months. Three treatments were analysed: pain medication, chemotherapy, and single and multiple fraction radiotherapy. For each of the three models, costs and utilities were calculated separately. For pain medication, costs were calculated on morphine medication combined with a laxative. Higher doses were used along the model. Utilities were set at 0.4 for the first 3 months and decreased by 0.05 every 2 months afterwards. For chemotherapy, the calculation of costs and utility used the outcome of a Canadian trial on mitoxantrone + prednisone [2.111]. The radiotherapy regimens were chosen from the recent RTOG 97-14 trial which studied the palliative effect of a single fraction of 8 Gy vs. 10 fractions of 3 Gy [2.6]. Costs were based upon true Medicare outcome, and utility was obtained from the study by van den Hout, et al. [2.112]. Table 2.12 shows the outcome of the three models: single fraction radiotherapy was the most cost-effective treatment with a cost-effective ratio of US $6.857 per QALY.

TABLE 2.12. MARKOV MODEL ON COSTS OF DIFFERENT TREATMENT MODALITIES FOR PAINFUL BONE METASTASES [2.110]

Treatment	Cost	Incremental cost	Effectiveness (QALM)	Incremental effectiveness (QALM)	Incremental cost effectiveness $ / QALY
Pain medication	$11 700		5.75		
SF radiotherapy	$11 900	$200	6.1	0.35	$6 857
MF radiotherapy	$13 200	$1 500	6.25	0.5	$36 000
Chemotherapy	$15 300	$3 600	4.93	-0.82	-

QALM= quality adjusted life per month

Figure 2.3 shows the cost effectiveness plan for both single fraction and multiple fraction radiotherapy with a 95% confidence ellipse comparing both treatments with analgesics alone. Unlike the multiple fraction regimen, most data points are below the willingness to pay line in quadrants I and IV for the single fraction regimen, making the single fraction regimen the best cost effective treatment.

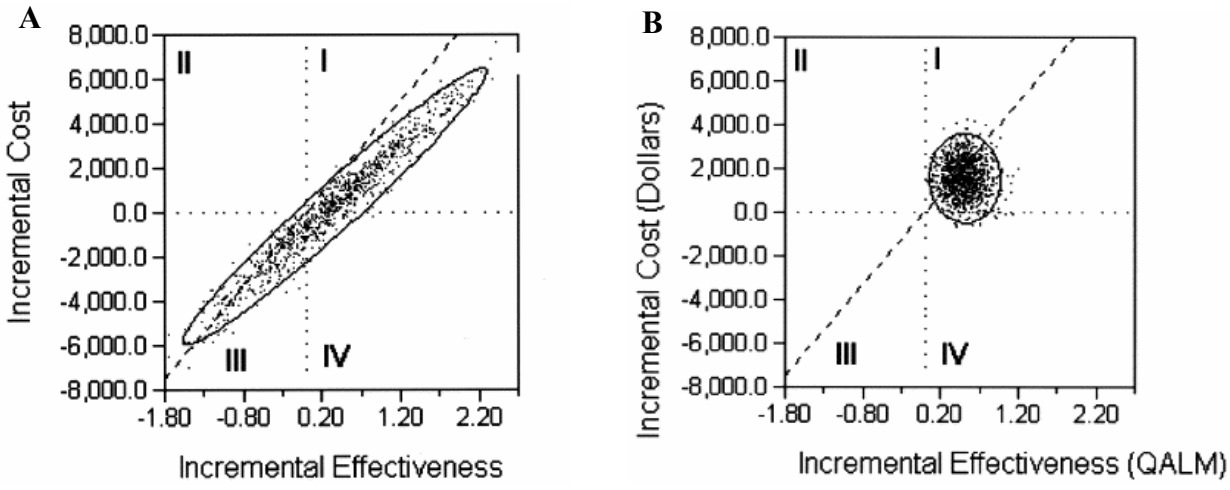

FIG 2.3. Cost effectiveness planes for pain medication versus SF radiotherapy (A) and versus MF radiotherapy (B) in the Markov model [2.110].

(3) In 2005, Pollicino et al published the results of an economic analysis on the patients included in the TROG 96.05 trial [2.113]. This study showed no significant benefit of multiple fraction radiotherapy over single fraction radiotherapy for neuropathic pain in 272 patients [2.114]. Pollicino et al performed a **cost minimization analysis** of both radiotherapy regimens. They looked at direct costs of treatment, i.e. including any retreatments during follow-up, analgesics, co-analgesics, and hospital admissions. Costs for radiotherapy were calculated using methodology from a previous study [2.115]. Use of medication was recorded prospectively during the trial. Data on hospital admission related to the treatment or because of pain were retrospectively obtained from the medical

records. Table 2.13 shows the results of this calculation: the single fraction treatment was AUS $1021 cheaper than the multiple fraction regimen, mostly due to difference in costs for the initial treatment, and costs incurred for hospital admissions. Next, a sensitivity analysis was performed, varying assumptions relating to individual cost components showing the incremental cost ranging from AUS $745 to AUS $1468.

TABLE 2.13. PRIMARY ANALYSES OF TOTAL COSTS in AUS $ [2.113]

Cost component	8 Gy / 1 fr.	20 Gy / 5 fr.	Average difference between 20 Gy / 5 fr. and 8 Gy / 1 fr.
Initial RT (protocol)	138	669	531
Retreatment	84	55	-20
Medication	192	229	37
Admissions related to RT or pain	1411	1893	482
Total average costs per patient	1825	2846	1021

(4) The most complete study comes from the Dutch Bone Metastasis Study Group (DBMS), a large prospective trial on 1157 patients that showed the equal effectiveness of a single fraction of 8 Gy compared to 24 Gy in 6 fractions [2.116, 2.117]. Van den Hout, et al. [2.112] performed a prospective **full societal cost utility analysis** on the DBMS database. For utility, survival on 1157 patients was registered by the data managers. For quality of life, the EuroQol utility [2.118] was registered in 13 weekly and 23 monthly patient based questionnaires. Of all 1157 patients, response to the questionnaires was 74%. Patients who received the single fraction regimen turned out to have an additional QALE of 1.7 week when compared to the multiple fraction patients (Table 2.14).

TABLE 2.14. QUALITY ADJUSTED LIFE EXPECTANCY (AVERAGE IN WEEKS, WITH STANDARD DEVIATIONS) [2.112]

	8 Gy × 1 (n=579)		4 Gy × 6 (n=578)		p-value[a]
Life expectancy	43.0	(35.2)	40.4	(34.4)	0.20
QALE ≤12 weeks	4.0	(3.9)	3.9	(3.9)	0.47
QALE	17.7	(24.0)	16.0	(23.8)	0.21

[a] standard two-sided unequal-variances t-tests

For the calculation of the costs, full societal costs were gathered for the first 3 months. Costs of radiotherapy consisted of direct medical costs (randomized schedule, retreatment), and non-medical costs (travel, time, out-of-pocket). For the treatment, in three radiotherapy centres a cost analysis was performed. Costs were allocated to 3 components: treatments, fractions and Gray (Table 2.15). Total costs of radiotherapy amounted to US $1838 for a SF and US $2448 for the multiple fraction regimen.

TABLE 2.15. MEDICAL COSTS OF A TYPICAL RADIOTHERAPY DEPARTMENT [2.112]

	Total costs		Allocation base		
	(in k$)		Treatments	Fractions	Gray
Personnel	1977	→[a]	63%	34%	3%
Equipment	1217	→	34%	35%	31%
Material	157	→	50%	41%	9%
Housing	1489	→	31%	68%	1%
Overhead	551	→	61%	35%	4%
Annual costs (in k$)	5391		2522	2379	490
Annual number			1503	24 640	61 600
Unit costs (in $)[b]			1678	96.55	7.95
Costs per 8 Gy × 1 schedule	$1838	←[c]	1 ×	1 ×	8 ×
Costs per 4 Gy × 6 schedule	$2448	←	1 ×	6 ×	24 ×

[a] Separate cost items are allocated to the allocation base(s) that they are proportional to
[b] Obtained by dividing the annual costs by the annual number, for each allocation base
[c] Obtained by multiplying the unit costs with the number of units of the schedule

A total of 166 patients filled out 6 bi-weekly questionnaires on other societal costs (medical: hospitalisation, consultations, medication, nursing, and non-medical: time, travel, out-of-pocket, domestic help, labour). Full societal costs are shown in Table 2.16. The overall difference in the costs to society (radiotherapy and other costs, both medical and non-medical) was estimated at $1753 per patient in favour of the single fraction schedule. The overall difference in medical costs (excluding the non-medical costs of radiotherapy and other non-medical costs) was estimated at $1344. Both differences were marginally significant (p=0.06 and p=0.09 respectively).

TABLE 2.16. COSTS PER PATIENT DURING THE FIRST 12 WEEKS (VOLUMES, AVERAGE COSTS IN $, AND STANDARD DEVIATIONS) [2.112]

		8 Gy × 1 (n=80)			4 Gy × 6 (n=86)		p-value[a]
Costs of radiotherapy		2438	(1019)		3311	(1682)	<0.001
Initial treatment		1838	(-)		2448	(-)	-
Retreatments ≤12 weeks	18%	466	(900)	5%	159	(539)	0.01
Time, travel, out-of-pocket	10 h	134	(213)	25 h	704	(1439)	<0.001
Other medical costs		2072	(3778)		3114	(6039)	0.18
Hospitalization	28%	914	(3091)	41%	2160	(5821)	0.08
Systemic therapy	61%	373	(718)	59%	247	(475)	0.19
Consultations	6.3	302	(554)	6.4	248	(234)	0.42
Pain medication		79	(114)		56	(113)	0.19
Other medication		322	(857)		247	(530)	0.51
Home nursing care	5 h	81	(251)	9 h	156	(501)	0.22
Other non-medical costs		190	(1230)		28	(1479)	0.44
Time, travel	8 h	94	(237)		130	(259)	0.35
Out-of pocket		127	(383)		64	(198)	0.19
Domestic help	42 h	438	(609)	43 h	482	(668)	0.65
(Un)paid labor	56 h	-468	(847)	77 h	-647	(1192)	0.26
Medical costs		**4376**	(3834)		**5720**	(6144)	0.09
Societal costs		**4700**	(4402)		**6453**	(7389)	0.06

[a] standard two-sided unequal-variances t-tests

Next, van den Hout et al tested the cost-effectiveness by comparing the net benefit, that is by testing whether the difference in costs was equal to the willingness-to-pay for the difference in QALYs. The acceptability curve (Figure 2.4) shows the p-value of this hypothesis for different values of the willingness-to-pay. From a societal perspective, the superior cost-effectiveness of the single fraction was shown at 5% significance level if one values a QALY between $5000 and $40 000. If one values a QALY at less than $5000 or more than $40 000, then superior cost-effectiveness of the single fraction schedule was still likely but not longer shown at the usual 5% significance level. For example, at $50 000 and $100 000 per QALY, the statistical significance was p=0.06 and p=0.09 respectively.

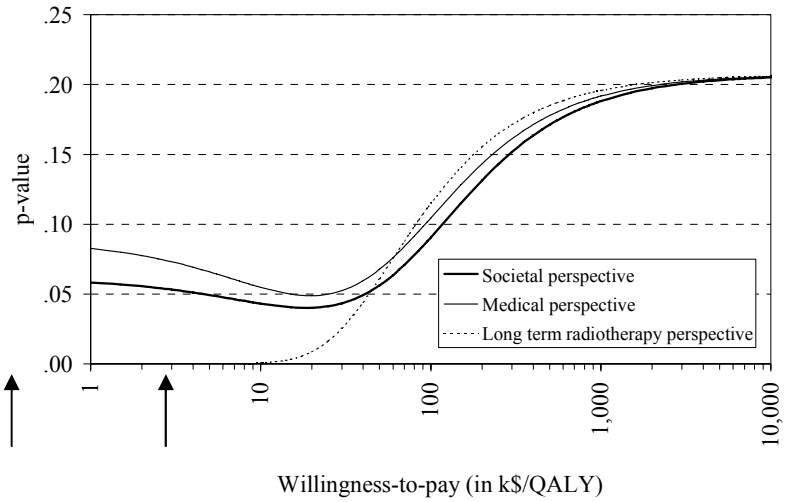

FIG. 2.4. Acceptability curves: p-value of the difference in net benefit WTP × QALYs − Costs, tested using standard two-sided unequal-variances t-tests [2.112].

(5) In the fifth study, Van der Giessen, et al. showed in a study that was carried out radiotherapy institutions in Europe, Africa, Latin America and Asia that a treatment fraction on a linac with functionality comparable to cobalt, costs roughly 50% more than cobalt therapy [2.119]. These variations depend more on differences in machine usage and costs of equipment than on national economic status.

In summary, all above mentioned studies are very heterogeneous in their design, comparing different outcomes and different time frames, so that definitive comparison of costs is not possible. However, most studies indicate that palliative radiotherapy for bone metastases provides good value for money when compared to other palliative treatment modalities and therefore, when radiotherapy units are available, single fraction or short-course radiotherapy should always be considered to treat pain arising from bone metastases.

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CHAPTER 3
RADIONUCLIDE THERAPY

3.1. Introduction

Radionuclide therapy is characterized by selective delivery of radiation doses to target tissues and by limited toxicity and few longterm effects. The treatment may be systemic or applied loco-regionally. In the first case, it combines the advantage of being selective like external beam radiotherapy or brachytherapy with that of being systemic like chemotherapy. The basis of successful radionuclide therapy is a good and selective concentration and prolonged retention of the radiopharmaceutical at the tumour site. The proven efficacy and minimal toxicity of this treatment modality make it very suitable for palliation in cancer patients. In general the treatment is well tolerated by patients and longterm follow up studies have demonstrated that radionuclide therapy carries a lower risk of leukaemia and second cancers than chemotherapy and external beam radiotherapy. A great number of applications of and indications currently prevail and there are many developments for new applications in the shortterm and in the longterm [3.1]. Radionuclide bone therapy is just one of the many applications in therapeutic nuclear medicine and has been around for 70 years. The use of Phosphorus-32 therapy dates back to 1936 [3.2] and that of Strontium-89 to 1941 [3.3]. Radionuclide bone therapy may be the treatment of bone metastases using specific tumour-seeking radiopharmaceuticals; bone therapy can also be the treatment of primary bone tumours, e.g. osteosarcoma, where the bone-seeking radiopharmaceutical behaves like a tumour-seeking agent, targeting the tumour-produced osteoid of not only the primary tumour and its skeletal metastases, but also the extra-osseous metastases. The third type is therapy using bone-seeking radiopharmaceuticals for the palliation of painful skeletal metastases. In contrast to radionuclide tumour therapy, in which the radiopharmaceutical is incorporated into or fixated to the tumour cell, this form of bone therapy targets the reactive osteoblastic reaction in the normal bone directly adjacent to the metastasis, which is generally the cause of pain. This review will focus on the latter application, i.e. palliative treatment of painful skeletal metastases using bone-seeking radiopharmaceuticals.

3.2. Radiopharmaceuticals

Requirements for an optimal therapeutic radionuclide agent for the palliation of painful bone metastases are:

- selective uptake and prolonged retention at metastatic sites in contrast to normal bone (in other words a high tumour-to-nontumour ratio);
- rapid clearance from soft tissues and normal bone;
- the biodistribution to be predicted by routine bone scintigraphy;
- a simple production process;
- radiochemical stability;
- easily transportable;
- readily available with good distributor logistics;
- cost effectiveness;
- lack of toxicity;
- radiation safety.

Table 3.1 shows the available radionuclides for bone therapy and their physical characteristics.

Phosphorus-32, applied as orthophosphate, and Strontium-89, as chloride, are pure β-emitters with a relatively long physical half-life. Rhenium-186 hydroxyethylidene-diphosphonate (HEDP), Rhenium-188 HEDP and Samarium-153 ethylenediaminetetramethylene-phosphonate (EDTMP) have considerably shorter half-lifes and γ- in addition to β-emissions, which enable post therapy scintigraphic imaging and dosimetry. On the other end of the spectrum of range are Tin-117m diethylenetriaminepentaacetic acid (DTPA) and Radium-223 phosphate, which, due to the conversion electrons and alpha emissions, respectively, have a short and ultrashort path length.

TABLE 3.1. AVAILABLE RADIOPHARMACEUTICALS FOR BONE THERAPY AND THEIR PHYSICAL CHARACTERISTICS

Radionuclide	Chemical form	Phys. half-life	Max. energy	Max. range	γ-emission
^{32}P	orthophosphate	14.3 d	β 1.7 MeV	8.5 mm	none
^{89}Sr	chloride	50.5 d	β 1.4 MeV	7 mm	none
^{186}Re	HEDP	3.7 d	β 1.07 MeV	5 mm	137 keV
^{188}Re	HEDP	16.9 h	β 2.1 MeV	10 mm	155 keV
^{153}Sm	EDTMP	1.9 d	β 0.81 MeV	4 mm	103 keV
^{117m}Sn	DTPA	13.6 d	CE 0.16 MeV	0.3 mm	159 keV
^{223}Ra	phosphate	11.4 d	α 5.78 MeV	<10 μm	154 keV

The choice of radiopharmaceutical is based upon the desired physical half-life, the extent of metastatic disease, the size of the lesions (in relation to the range of the radionuclide), the bone marrow reserve and the availability and cost of the radiopharmaceutical. For instance, patients with a limited number of painful skeletal metastases, good bone marrow reserve and manageable pain may be treated with Sr-89-chloride or P-32-orthophosphate. On the other hand, in patients with extensive skeletal metastases, limited bone marrow reserve, and/or in whom early response is mandatory, the use of Re-186-HEDP or Sm-153-EDTMP is more appropriate. Using recommended administered doses (see below), all these radiopharmaceuticals carry a low risk of toxicity, with the exception of P-32, which is associated with more haematological effects. Dosimetric assessment for some of these agents revealed mean absorbed radiation doses of 35 Gy at tumour sites compared to 2.6 Gy to normal bone and 1.7 Gy to the bone marrow for 150 MBq Sr-89-chloride, 40 Gy to the tumour site, 1.8 Gy to normal bone and 1.7 Gy to marrow for 1295 MBq Re-186-HEDP, and 87 Gy to the tumour, 17.5 to normal bone and 4 Gy to bone marrow for 2590 MBq Sm-153-EDTMP.

3.3. Indications and patient selection

Indications for radionuclide bone therapy are treatment refractory painful skeletal metastases of the blastic or mixed type from prostatic carcinoma and breast carcinoma (established indications), as well as any other tumour with intense uptake around painful metastases on the bone scintigram. The most common explanation for treatment failure is inappropriate patient selection. Patients must undergo bone scintigraphy using Tc-99m-methylene diphosphonate (Tc-99m-MDP) shortly before planned treatment administration. Foci of increased uptake on the bone scan must be correlated with the sites of the patient's symptoms to ensure that the pain can be attributed to osteoblastic bone metastases. Other sources pain, such as vertebral collapse, nerve root entrapment, fracture and visceral pain, will not respond to radionuclide therapy. Optimal results are obtained where pain sites match areas of increased Tc-99m-MDP uptake that are likely to concentrate and retain bone-seeking radiopharmaceuticals. Response is less predictable in patients with a predominantly osteolytic pattern of skeletal metastasis, presumably because poor uptake and retention result in a lower metastatic absorbed radiation dose. Contra-indications for radionuclide bone therapy are myelosuppression, impaired renal function, pregnancy, spinal cord compression and impending bone fractures. Patients should be haematologically and biochemically stable before treatment. Recommended haematological parameters are: haemoglobin >90 g/L, white blood cell count $>4 \times 10^9$/L and platelet count of $>100 \times 10^9$/L. Haemopoietic reserve can be assessed by correlating the peripheral full blood count with tumour extent on conventional bone scintigraphy. Diffuse infiltration, the superscan appearance, or increased uptake in the proximal long bones indicate extensive marrow replacement by tumour and are unfavourable prognostic features. Poor renal function will delay clearance of most bone-seeking radiopharmaceuticals, leading to a higher whole-body dose and potentially increased toxicity. Modest renal impairment is common in the elderly population with prostatic carcinoma, but outflow obstruction at the vesico-ureteric junction or bladder neck should be treated appropriately before radionuclide administration. Recommended renal function parameters are: urea <12 mmol/L, creatinine <200 mmol/L. Risk of pathologic fracture and acute spinal cord compression should be regarded as a surgical or radiotherapy emergency and not be treated with radiopharmaceuticals. Urinary incontinence presents a contamination risk and should be managed by bladder catheterization before radiopharmaceutical administration. Re-treatment may be considered in patients who have recurrence or new sites of pain, if they had a good response to previous radionuclide bone therapy and if the conditions described above are met [3.4, 3.5].

3.4. Procedural aspects

3.4.1. Preparation

A number of conditions should be met in preparation of any therapeutic radiopharmaceutical to be administered for bone therapy. Patients must undergo bone scintigraphy within 14 days prior to treatment, on the basis of which it is confirmed that pain sites correspond to areas of increased tracer uptake (pain mapping). Equally important is to have a recent assessment of both haematological and renal function parameters. Subsequently the therapeutic procedure is planned, i.e. ordering and timely delivery of the radiopharmaceutical, scheduling the administration and, if applicable, post therapy scintigraphic imaging within the nuclear medicine department. Prior to the administration of the radiopharmaceutical, patient information should be given both orally and by a written pamphlet to be created by the local radiation protection officer together with the nuclear medicine department, which may be

slightly different for each radiopharmaceutical used. The patient information should at least include:

- an explanation of the therapeutic procedure
- an estimate as to when pain relief may be expected (varying per radiopharmaceutical)
- a warning that a transient flare effect of pain may occur and that, therefore, analgesic medication must be continued
- radiation protection guidelines, e.g. regarding contact with partner, pregnant women, children
- hygienic measures (e.g. micturation while seated, how to deal with a contamination)
- advice that, in case of hospitalization or other medical care within 30 days, the physician must informed, as the therapy may influence other scintigraphic procedures
- advice, when travelling shortly after therapy, to carry a medical declaration and radiation safety certificate (see annexure), because of airport security checks.

3.4.2. Administration and recommended administered dose

For the administration of therapeutic amounts of radionuclide agent it is important NOT to inject the radiopharmaceutical directly into a vein, but through a secure intravenous line or indwelling butterfly needle in connection with a 3-way tap. After the line has been tested by injecting a little 0.9% saline solution, the radiopharmaceutical is administered as a slow or bolus i.v. injection. Great care should be taken to avoid any extravasation. Subsequently the i.v. line or butterfly needle is flushed using 0.9% saline solution and removed and all used materials are to be disposed of according to radiation protection guidelines. Recommended administered doses for therapeutic use of the various bone seeking agents are:

- P-32-orthophosphate: 450 MBq; retreatment not before 3 months
- Sr-89-chloride: 148 MBq; retreatment not before 3 months
- Re-186-HEDP: 1.4 GBq; retreatment not before 2 months
- Re-188-HEDP: 2.5-3.3 GBq; retreatment interval not established
- Sm-153-EDTMP: 37 MBq/kg; retreatment not before 2 months
- Sn-117m-DTPA: 2–10 MBq/kg; retreatment not before 2 months [3.4, 3.5].

3.5. Efficacy

A great number of studies using bone-seeking radiopharmaceuticals for the palliation of painful bone metastases have been published. As the selection of patients as well as the chosen parameters of response has not always been identical great variation in observed response rates is noted. The more one confines the treatment to patients with multiple painful skeletal metastases of the blastic type, without mechanical impairment (fracture, cord compression), the better the response rates tend to be. In general it can be stated, that the overall benefit (i.e. any degree of palliative effect) from all these treatments is around 75% and that about 25% of the patient have complete response, i.e. becoming free of pain. Table 3.2 summarizes the range of the published response rates for each of the radiopharmaceuticals separately, the overall response ranging 45–92% and the complete response ranging 10–30%. Also the reported time to the onset of pain relief and the duration of response is shown: although the onset of response is later (1–4 weeks after administration) for the longer lived isotopes, such as P-32, Sr-89 and Sn-117m, the time to response of the Re-186, Re-188 and Sm-153 labelled compounds is 2–7 days, i.e. comparable to that of external beam

radiotherapy. The duration of response also varies somewhat, but generally ranges 2–6 months.

TABLE 3.2. EFFICACY OF RADIONUCLIDE BONE THERAPY REPORTED IN THE LITERATURE [3.4–3.19]

Pain palliation→	**Overall response**	**Complete response**	**Time to response**	**Duration of response**
^{32}P-phosphate	50–87%	20%	5–14 days	2–4 months
^{89}Sr-chloride	45–90%	10–22%	2–4 weeks	3–6 months
^{186}Re-HEDP	50–92%	20%	2–7 days	2–4 months
^{188}Re-HEDP	64–77%	22–26%	2–7 days	2–6 months
^{153}Sm-EDTMP	65–80%	n.a.	2–7 days	2–4 months
^{117m}Sn-DTPA	60–83%	30%	2–4 weeks	n.a.

Several prospective studies comparing therapeutic bone-seeking radiopharmaceuticals with a placebo have demonstrated that the palliative effect can be attributed to the targeted radiation rather than the formulation. In a double blind crossover study in 32 patients the palliative effect of Sr-89-chloride was superior to that of stable strontium (Sr-88) [3.20]. Two other studies similarly demonstrated more pain relief by Re-186-HEDP therapy compared to placebo, as well as a diminished requirement of additional external beam radiotherapy [3.21, 3.22]. Also Sm-153-EDTMP was demonstrated to produce more pain relief that its non-radioactive counterpart, Sm-152-EDTMP in two comparative placebo studies [3.23, 3.24]. Few comparative studies of radionuclide agents have been published. Comparing the effects of 444 MBq P-32 given orally with those after intravenous administration of Sr-89-chloride complete pain relief was found to be similar (7/16 vs 7/15 patients), but more haematological toxicity was observed after P-32 [3.25]. Dafermou et al., comparing 527 treatments with Sr-89-chloride with 83 treatments with Re-186-HEDP, found no difference in efficacy and toxicity, although the duration of response was slightly longer for Sr-89 [3.26]. Even one study, comparing 3 bone-seeking radiopharmaceuticals (Re-186-HEDP, Re-188-HEDP and Sr-89-chloride) could not demonstrate differences in palliative response and toxicity [3.27].

3.6. Cost aspects

There are very scarce data on cost-effective evaluation of radionuclide treatment for metastatic bone pain. Most of the data published so far are cost-minimization analyses based on the micro-approach of health economics, simply comparing costs of two different treatments with equivalent outcomes. An adequate cost-effectiveness study seems to be quite difficult to perform, given the many economic variables related to costs of therapy (technologies, supplies, preparation, administration, monitoring, etc.), costs of treating side effects incurred as a result of therapy, costs utilized on information from referral processes, and costs utilized or saved during additional years of life, if extended by the therapy. There is a very wide range of costs for radionuclide treatment in different locations and countries

($3000–$8000 in the USA, $2400 in Korea, $100 in China, $1000–$1500 in Europe) in 2005. However, cost savings resulting from radionuclide treatment have been reported, due to diminishing use of narcotic opioids in the USA [3.28], and also to replacement of external beam radiation therapy (EBRT) or in conjunction with EBRT [3.29, 3.30].

3.7. Beyond palliation: combination of radionuclide therapy with other modalities

Since the early introduction of radionuclide therapy for palliation in patients with metastatic bone disease, this issue has raised attention in view of some anedoctical observations on regression of lesions seen on the bone scan following such therapy and/or of prolonged survival, especially in patients with hormone-refractory prostate cancer. However, the lack of specific clinical trials specifically designed to address this issue has for many years eluded expectations that such form of treatment might definitely demonstrate some 'true' therapeutic potential in addition to its ascertained beneficial effects on bone pain [3.31]. When reviewing prior literature in this scenario, one has to consider that different parameters have been employed by different authors for defining 'objective' response to treatment as opposed to simple palliation of bone pain. These parameters have included significant reduction (>50% versus baseline) in the serum levels of the specific tumour marker (PSA) [3.32], prolonged time to appearence of new skeletal metastatic sites [3.33], reduction in the number of subsequent treatments (such as repeated radionuclide therapy or EBRT) required for local control of new metastatic lesions, prolonged survival (either progression-free and/or overall survival) [3.34], etc. In terms of biochemical tumour markers, some reduction in serum PSA levels has been documented in a recent multicenter European clinical trial where 13% of the patients treated only with a standard dose of Sr-89 exhibited such biochemical response (versus 10% of the patients treated with EBRT) [3.35]. This observation is in line with prior reports indicating definite biochemical response in a sizable proportion of patients treated with Sr-89 [3.36], not seldom associated with reduction in the metastatic skeletal involvement as assessed by whole-body bone scintigraphy [3.37]. In this regard, occurrence of a significant biochemical response to Sr-89 treatment (PSA reduction) appears to represent a reliable indicator of improved survival following such therapy [3.38]. Additional, though indirect, markers of objective response to treatment with Sr-89 include biochemical indicators of bone resorption, such as the pyridinium collagen cross-links excreted in urine. By using these surrogate markers, Papatheofanis has demonstrated that Sr-89 therapy significantly slows down bone resorption up to at least 6 months after treatment, while such effect was not observed in patients treated with conventional analgesics and EBRT [3.39]. Increasing awareness that radionuclide treatment might ensue some therapeutic effect beyond simple palliation has prompted several groups to explore the possibility of achieving some synergistic effect by the combination of such treatment with some other anti-tumour agents, especially chemotherapy agents. Choice of the chemotherapy agent for combination with radionuclide therapy must consider that there some well-known radiosensitizers that do not, however, possess anti-tumour activity in patients with metastatic prostate cancer, and that a compromise should be found by choosing chemotherapy agents with ascertained anti-tumour activity in these patients. In this regard, there are several compounds that target either DNA and/or non-DNA targets, including 5-fluoro-uracil, analogs of platinum, gemcitabine, DNA-topoisomerase-I targeting drugs, and non-DNA targeting molecules [3.40]. Obviously, the combined use of two anti-tumour agents (radionuclide and chemotherapy) both entailing some degree of toxicity (mostly bone marrow depression) has raised concerns about possible additive adverse activity with potentially severe side effects. This issue has been addressed by a preliminary study indicating the feasibility and tolerability of combined therapy with Sr-89 (repeated every three months) and doxorubicin in hormone-refractory metastatic prostate cancer (as a collateral finding, this non-randomized study also demonstrated definite clinical

benefit and significant PSA response to such combined therapy) [3.41]. Once the concern of potentially severe side effects resulting from combined treatment had been overcome, a subsequent randomized clinical trial by the same group addressed the specific issue of objective benefit possibly deriving from such combined protocol [3.42]. This study disclosed definite advantages of the combined treatment not only in terms of PSA response and time to progression, but also in terms of overall survival. In fact, median survival of patients treated with both Sr-89 and doxorubicin was 27.7 months, significantly longer than median survival in patients treated with doxorubicin alone (16.8 months, $p=0.0014$), not to mention median survival of 11.1 months in patients receiving neither of the two regimens. These findings laid the ground to formulate the hypothesis that combined treatment was especially effective because it permitted to target both the so-called 'seed' (prostate cancer cells, by the chemotherapy agent) and the 'soil' (the bone matrix environment, by the bone-seeking radionuclide) of the metastatic site. An independent study explored the potential objective benefits of Sr-89 therapy combined with cisplatin [3.43], based on prior reports on the possible synergistic effect metabolic radiotherapy with platin compounds [3.44–3.46]. Although this study demonstrated significant advantages of combined therapy over Sr-89 alone concerning overall pain relief ($p<0.01$), duration of pain relief ($p=0.02$), median survival without new painful sites ($p=0.04$), and progression of bone disease ($p=0.01$), it failed however to show significantly prolonged median survival in the group receiving combined therapy versus the group receiving Sr-89 alone. Similarly disappointing results in terms of survival benefit were obtained by Pagliaro et al. with a combination protocol based on Sr-89 and gemcitabine [3.47]. Although most of the published reports on possible objective benefit deriving from combined chemotherapy and radionuclide therapy of bone metastatic prostate cancer concern strontium-89, preliminary data not yet published in full suggest that also for Sm-153-EDTMP combination protocols with chemotherapy agents (either estramustine phosphate or mitoxantrone plus prednisone) significanly prolong survival of patients with hormone-refractory disease, from a median of 16 months to a median of 30 months ($p=0.002$) [3.48]. Growing interest in this field is demonstrated by the fact that, considering the USA alone, there are currently at least five different ongoing clinical trials on bone metastatic prostate cancer involving Sm-153-EDTMP in combination with either docetaxel or paclitaxel (source: Cytogen Corporation, Princeton, NJ, USA). Furthermore, clinical trials involve a combination regimen of Sm-153-EDTMP with paclitaxel and bevacizumab in patients with breast cancer metastatic to the bone or this bone-seeking radiopharmaceutical combined with other anti-tumour agents in patients with myeloma (three protocols), or in patients with osteosarcoma (two protocols). This latter application is based on promising results obtained with the combination of high-dose Sm-153-EDTMP (30 mCi/kg body weight versus the standard dose of 1 mCi/kg) with gemcitabine in patients with advanced osteosarcoma [3.49]. Clearly, the use of Sm-153-EDTMP at high doses, as done in the osteosarcoma trial as well as in some of the myeloma trials, involves utilization of stem cell harvesting for bone marrow salvage after treatment.

Hopefully, the ongoing trials will contribute to answer some of the still open questions concerning radiometabiolic therapy of bone metastases, as summarized by Silberstein in a recent review of this matter [3.50] as follows:

(i) shall these radionuclide treatments be used also to treat painless osteoblatic metastases in order to delay the onset of pain?

(ii) do other agents besides Sr-89 delay the onset of new or recurrent bone pain?

(iii) what are the best combinations of radiopharmaceuticals, hormones, and chemotherapy to treat painful bone metastases, not only to reduce pain, but also to prolong life?

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CHAPTER 4
FUTURE DEVELOPMENTS: NOVEL AND TUMOUR SPECIFIC RADIOPHARMACEUTICALS

4.1. Short range isotopes

4.1.1. Sn-117m (Sn-117m-DTPA, Sn-117m-Pentetate)

The premise that the efficacy of other bone-seeking radionuclides is limited by myelotoxicity has stimulated interest in the therapeutic potential of short-range electron emitters. The chelate Sn-117m-diethylenetriaminepentaacetic acid (Sn-117m-DTPA) is an experimental radiopharmaceutical undergoing evaluation for treatment of painful bone metastases [4.1]. Sn-117m(4) decays by the emission of low-energy conversion electrons (Emax 0.16 MeV) and a low-abundance 159 keV γ-photon. The physical half-life is 13.6 d. Optimal blood and soft tissue clearance is achieved by chelation with diethylenetriaminepentaacetic acid (DTPA). The energetic conversion electrons have a very short range in soft tissue (max. 0.3 mm), which may explain the low incidence of myelosuppression seen with Sn-117m-pentetate. Sn-117m is injected as the pentetate (DTPA) chelate and has no affinity for hydroxyapatite. The mechanism of localization is postulated as precipitation of stannous oxide on bone surfaces or by a hydrolysis reaction with hydroxyapatite. Dosimetric studies in a mouse femur model determined the mean femoral marrow absorbed dose as 0.043 cGy/MBq compared with a mean absorbed dose to bone of 1.07 cGy/MBq [4.2]. Human studies confirm biexponential whole-body clearance after intravenous Sn-117m-DTPA injection. The average soft tissue biologic half-time is 1.45 d, accounting for 22.4% of the administered activity. The bone component accounts for 77.6% of injected activity and shows no biologic clearance, and 22.4% of administered activity is cleared renally. Peak bone uptake occurs in normal bone within 24 h, but metastatic skeletal uptake occurs slowly over 3–7 d [4.3]. The first phase 1 activity escalation study conducted over the activity range of 66–573 MBq reported symptom benefit in 9 of 10 evaluable patients with no significant myelotoxicity [4.4]. A later phase 1/2 activity escalation study in 47 patients with painful bone metastases reported a 75% overall pain response (range, 60%–83%), with complete pain relief in 30% [4.5]. There is no dose–response relationship; the onset of pain relief is also much earlier than that with the other agents described. At doses of ≥444 MBq (≥12 mCi) (per 70 kg body weight), pain palliation has been noted as early as <1 wk after treatment [4.5]. The typical response time was 19 ± 15 d using activities of ≤5.29 MBq/kg and 5 ± 3 d in patients receiving activities of ≥6.61 MBq/kg. Myelotoxicity was minimal, with 1 patient experiencing grade 3 white cell count toxicity. The outcomes of additional trials are awaited.

4.1.2. Radium-223 (Ra-223-chloride)

Recent attention has focused on the α-emitter Ra-223, administered as Ra-223-chloride (Ra-223-Cl_2). Like calcium, radium has a natural affinity for metabolically active bone. The physical half-life is 11.4 d. Blood clearance is rapid after intravenous administration [4.6]. Peak skeletal uptake occurs within 1h of injection, with no subsequent redistribution [4.7]. Unlike most other bone-seeking radionuclides, excretion is predominantly via the gastrointestinal tract, with less than 10% renal clearance [4.7]. Ra-223 decays by the emission of 4 α-particles via daughter isotopes to stable Pb-207. The total decay energy is 28 MeV. Ra-223-Cl_2 is selectively concentrated on bone surfaces relative to soft tissues in murine models, leading to relative marrow sparing. Limited absorbed dose estimates indicate a tumour-to-marrow ratio of 30:1. Preclinincal and pilot phase I activity-ranging studies have failed to demonstrate limiting toxicity. Temporary myelosuppression is reported but has not exceeded

WHO grade 1, even at high activities (200 kBq/kg) in heavily pretreated patients. The low-grade toxicity reported is attributed to the short (100-μm) α-particle range in tissue. Common side effects include diarrhea and nausea or vomiting, which appear activity related in a small phase 1 study. Phase 1 data suggest superior response after fractionated administration compared with a single high-activity therapy. Phase 2 randomized, placebo-controlled studies are in progress.

4.2. Radiolabelled peptides and antibodies

Breast, prostate, lung, thyroid, renal cancers, lymphomas and other tumours develop bone metastases by haematogenous dissemination of cancer cells and, aside from bone-seeking tracers, a number of tumour-specific radiopharmaceuticals have been proposed for the treatment of metastatic spread [4.8]. Clinically established are now monoclonal antibodies for the treatment of lymphomas (NHL). However, significant bone marrow involvement is more often a contraindication for radioimmunotherapy due to severe bone marrow depression which can occur when using anti-CD 20 antibodies labelled with Y-90 or I-131 due to the high energy of these β-emitters (unwanted cross-fire effect). In the field of the peptide receptor radionuclide therapy, several radiopharmaceuticals e.g. radiolabelled somatostatin analogues like Y-90-DOTATOC or Lu-177-labelled DOTATATE have recently become available for the treatment of neuro-endocrine tumours [4.9]. These novel radiopharmaceuticals (none of them is up to now officially approved) have demonstrated significant anti-tumour responses mainly concerning liver and lymph node metastases or for the treatment of unresectable primary tumours. Bone metastases are seen very frequently in advanced neuro-endocrine tumours, and in some patients cause severe pain and myelocompression. Preliminary results in patients with widespread bone metastases (e.g. from paragangliomas or phaeochromocytomas which do not take up ^{131}I-MIBG) have shown impressive improvement of symptoms and reduction of osseous pain without severe myelosuppression. Therefore, small molecules (like peptides or engineered antibodies) labelled with short-range beta, alpha or electron emitters might be less myelotoxic and certainly more effective in tumour cell killing then bone-seeking tracers. The challenge is open to enhance the therapeutic efficacy of these new radiopharmaceuticals with the aim of controlling and reducing the cancer mass and relieving pain from bone metastases, by using different protocols in prospective trials (e.g. higher doses, association with other chemotherapeutics, combination with external beam radiation).

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CHAPTER 5
RATIONALE FOR USE OF BOTH MODALITIES

Table 5.1 represents a consensus view of the committee of radiotherapy and nuclear medicine consultants for a rationale when and how to use the two treatment modalities for the palliation of painful skeletal metastases in various ways of presentation.

TABLE 5.1. RATIONALE FOR THE USE OF EXTERNAL BEAM RADIOTHERAPY AND RADIONUCLIDE BONE THERAPY FOR THE PALLIATION OF METASTATIC BONE PAIN

Patient's Specific Indication	**External Beam Radiotherapy**	**Radionuclide Therapy**
Types of metastases:		
- Osteoblastic	Yes	Yes
- Osteolytic	Yes	No
- Mixed type	Yes	Yes
Number of metastases:		
- Solitary	Yes, local field	No
- Limited	Yes, local field	Yes, preferably longer T1/2
- Extensive	Yes, widefield	Yes, preferably shorter T1/2
Tumour type	All	All, if osteoblastic metastases
Risk of fracture	Yes	No
Spinal cord compression	Yes	No
Expected survival:		
- Short (<3 months)	Yes	Yes, preferably short T1/2
- Longer (>6 months)	Yes	Yes, longer T1/2 possible

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