Chapter 2
Natural History, Prognosis, Clinical Features and Complications of Metastatic Bone Disease

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Abstract The survival and prognosis of cancer patients with metastatic skeletal disease varies widely and depends on many factors including the histologic type and grade of the primary tumor, performance status and age of patients, presence of extraosseus metastatic disease, level of tumor markers and extend of skeletal disease. Bone metastases are inevitably associated with considerable morbidity and suffering, and severe complications such as pain, pathological fractures, spinal cord or nerve root compression, impaired mobility, bone marrow infiltration and hypercalcemia of malignancy. In the current chapter all aforementioned complications are thoroughly discussed, giving emphasis to associated symptomatology, clinical features and patient evaluation. Symptom clusters that occur in patients with bone metastases before and after treatment are also presented. Such symptoms include pain, depression, fatigue, drowsiness, anxiety, shortness of breath, nausea, poor sense of well being and poor appetite.

Keywords Bone metastases • Natural history • Complications • Clinical features • Spinal cord compression • Symptom clusters • Hypercalcemia • Quality of life • Pathologic fractures

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2.1 Introduction

Bone metastases are not only common in the event of malignancy, but their development is of particular clinical importance, since they can bring about severe complications such as pain, pathological fractures, spinal cord compression and hypercalcemia [1, 2]. Such events may be detrimental not only for the quality of life and performance status of affected patients, but may also be life threatening [3]. In this chapter we discuss the natural history, prognosis, clinical picture and complications of metastatic bone disease. Symptom clusters occurring in cancer patients with metastatic bone lesions are also presented.

2.2 Natural History and Prognosis

Due to the high prevalence, marked osteotropism and the relatively long clinical course of breast and prostate cancer, bone metastases are most often seen in patients with such malignancies. Bone metastases are also frequent in other tumors such as lung, kidney and thyroid. The survival from the time of development of bone metastases varies considerably among the different types of tumors. In the case of prostate and breast cancer, the median survival from the time that bone metastases are diagnosed is measured in years [4–6], whereas the corresponding survival in patients with advanced lung cancer is measured in months [7, 8].

Through several studies it was shown that certain tumor characteristics were associated with an increased risk of developing either bone or extaosseus metastases. In breast cancer patients the incidence of metastases to bone was found to be significantly higher in tumors which produce parathyroid hormone related peptide (PTHrP) [9] and are either estrogen receptor positive [10] or well differentiated [4, 11]. A significant association between histological high grade tumors and a development of intrapulmonary, liver and para-aortic lymph node metastases has also been reported [11]. In a different study by James JJ et al., a significant correlation between the development of skeletal metastases and the degree of lymph node involvement by the primary tumor was also found [12].

In a trial involving 2,240 consecutive patients with localized breast carcinoma, 30 % relapsed after a median follow up period of 5 years, with 8 % developing metastasis to bone. The median survival after the recurrence in bone was 20 months, whereas the survival in women who developed metastasis to liver was only 3 months [4]. The survival of patients with bone metastases from breast cancer was also influenced by the subsequent formation of extraosseus metastases. The median survival of such patients was shown to be 1.6 years as compared to 2.1 years for patients with metastases confined to the skeleton [13]. In the same study it was found that older, post menopausal women with lobular carcinoma or ductal grade III tumors were more likely to have disease that remains confined to skeleton [13]. The same was true for women with minimal axillary lymph node involvement [13]. In a recent trial

Table 2.1 Prognostic factors in patients with metastatic breast or prostate cancer

Primary cancer	Breast	Prostate
	Extraosseus metastases	Performance status
	Estrogen receptor status	Histologic grade
	Metastasis free survival	Baseline prostatic specific antigen
	Performance status	Hemoglobin level
	Age	Alkaline phosphatise
	Serological tumor marker levels	Lactate dehydrogenase
	Histologic type (lobular versus ductal)	Aspartate aminotransferase
	Histologic grade (ductal)	Extent of bone disease
	Bone metastases at presentation	Age
	Number of bone metastases	Gleason score
	Symptomatic skeletal metastases	Clinical stage

Data from James JJ et al. [12], Coleman RE et al. [13], Niikoura N et al. [14], Robson M et al. [15], Sabbatini P et al. [16], Eisenberger M et al. [17], Matzkin H et al. [18], Armstrong AJ et al. [19], He J et al. [20]

it was reported that the development of SRE's in patients with skeletal disease from breast cancer leads to a decreased 5 year survival as compared to patients with bone metastases alone (8.3 % versus 2.5 %) [6].

Survival in women with bone metastases is also dependent on other clinical and histopathological factors such as the metastasis free survival interval, additional sites of metastatic disease other than bone, estrogen receptor status, symptomatic skeletal disease, number of metastases and serological tumor marker levels [10, 12, 14]. Multivariate analysis has shown that all of these factors independently contributed to survival from the time of bone metastases formation [12]. In a different study by Coleman et al., multivariate analysis showed that age, menopausal status, bone disease at initial presentation and histological grade and type, were also important prognostic factors after the diagnosis of metastatic bone disease [13]. Important factors of good prognostic significance were lobular or ductal grade I or II carcinomas, age <70 years, disease free interval ≥3 years, bone disease at presentation and positive estrogen receptor status [13]. Established prognostic factors in women with bone metastases from breast cancer are presented in Table 2.1.

Patients with prostatic carcinoma also have a relatively long clinical course. In men with metastases confined to the axial skeleton, good performance status and under androgen blockade, the duration of disease control was found to be 4 years [15]. Survival in patients with metastatic prostatic cancer is dependent on several prognostic factors such as tumor grade, baseline prostate specific antigen (PSA), PSA doubling time, hemoglobin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gleason score, clinical stage, invasion of neighbouring organs, performance status, number of metastatic sites and extent of metastatic bone disease (Table 2.1) [15–20]. It may be worth to note that the extent of metastatic bone disease in prostatic cancer may be quantified by using the bone scan index (BSI). In this system each bone is evaluated individually and assigned a numeric score. The score represents the product of the percentage of the involved bone with

Table 2.2 Complications that may accompany metastatic bone disease

Pathological fracture
Bone pain
Hypercalcemia of malignancy
Nerve root compression
Impaired mobility
Surgery to bone
Radiation to bone
Spinal cord compression
Infiltration of bone marrow

tumor times the known weight of the bone that is derived from the reference man [21]. It has been shown that in patients with BSI values <1.4 %, 1.4–5.1 % and >5.1 %, median survivals were 18.3, 15.5 and 8.1 months respectively [16].

Survival in patients with multiple myeloma ranges from a few months to more than a decade [21]. With modern, intensive therapy involving autologous hematopoietic stem cell transplantation, the median survival is approximately 5 years [22]. Many prognostic factors have been reported in the scientific literature, the most important ones being albumin, beta2-microglobulin, chromosomal karyotype, renal function, hemoglobin, performance status, calcium, interleukin 6 (IL6), C-reactive protein (CRP), low plasma cell percentage in bone marrow and a positive response to treatment [21–23].

Renal cell cancer also shows a predilection to bone. Metastases from renal carcinoma are usually lytic in type, highly vascular and are associated with severe morbidity [24]. In a series with 209 patients with renal cell carcinoma, bone metastases developed in 22 % of patients and bone was the second commonest site of metastases after lung (37 %) [25]. In a recent study by Toyoda Y and co workers it was shown that median survival in patients with bone metastases from renal carcinoma was 12 months and overall survival at 2 years was 37 %. In the same study it was found that clinical features correlating with longer survival were a long interval between the time of diagnosis and development of bone metastases (greater than 24 months) and the absence of extraosseus metastatic disease [26]. The median survival of patients with none of the above favorable factors was 5 months and for those with both factors 30 months [26].

2.3 Morbidity and Complications of Metastatic Bone Disease

Bone metastases are accompanied by considerable morbidity and suffering. About two thirds of patients with breast cancer and metastases to bone will subsequently develop complications such as pain, pathological fractures, spinal cord or nerve root compression, impaired mobility, bone marrow infiltration and hypercalcemia of malignancy [27–29]. Table 2.2 summarizes the potential complications associated with bone metastases. From the presented complications (Table 2.2), pathological fractures, hypercalcemia of malignancy, spinal cord compression, surgery to bone

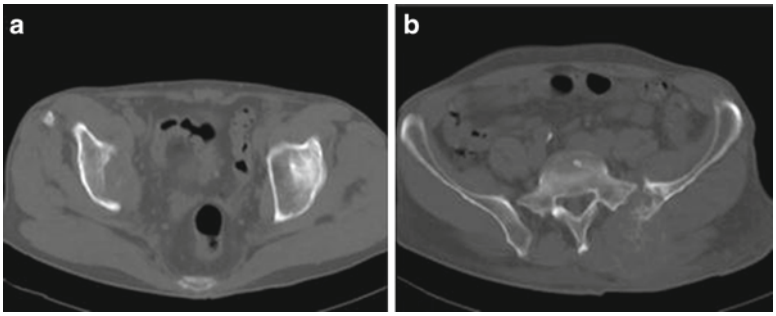

Fig. 2.1 Lytic bone metastases in the *right* (**a**) and *left* (**b**) iliac bones in two patients with renal carcinoma (This figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

and radiation to bone are known as skeletal related events (SREs). These events are composite end points used in the majority of trials involving treatment with bisphosphonates.

Pain and impaired mobility are evident in 65–75 % of patients with bone metastases [30] and metastatic bone lesions have been reported to be the commonest cause of cancer-related pain [31]. Bone pain may be nociceptive [32, 33], or neuropathic [32–34]. In the former case pain is produced via simulation of nociceptors in the endostium by chemical mediators such as prostaglandins, leukotrienes, substance P, bradykinine, interleukins 1 and 6, endothelins and tumor necrosis factor-a (TNF-a). Nociceptive pain may also result due to stretching of periostium resulting from tumor infiltration or increase in size, or fracture. Neuropathic pain may result from direct infiltration and destruction of nerves by tumors.

In two recent trials pain was found to be the major factor affecting the quality of life and performance status of cancer patients with bone metastases [35, 36]. The level of morbidity differed between patients with different types of metastatic bone lesions (lytic, mixed, sclerotic) [35]. Figures 2.1, 2.2, and 2.3 present typical examples of lytic, mixed and sclerotic bone metastases. Patients with osteolytic lesions had the highest mean pain scores with 8.1 points (visual analogue scale, 0–10) and the least mean scores for quality of life (QOL-EORTC C30, physical functioning scale, 0–100) and Karnofsky performance status (KPS, 0–100) with 31.4 and 58.6 points respectively. This group of patients was also found to have the highest percentage and mean opioid consumption (measured in daily oral morphine equivalents, mg) and the least mean bone density within skeletal lesions with 116.3 Hounsfield units (HU, measured by Computer Tomography). On the contrary the group with osteosclerotic bone lesions had the least mean pain score with 4.6 points, the highest mean scores for QOL and KPS with 61.1 and 66.6 points respectively, the least percentage and mean opioid requirement and the highest mean bone density with 444 HU. Table 2.3 presents the mean values of the clinical and radiological evaluations of the three groups of patients taking part in the study [31]. Interestingly, this study also showed that bone density had a strong, negative,

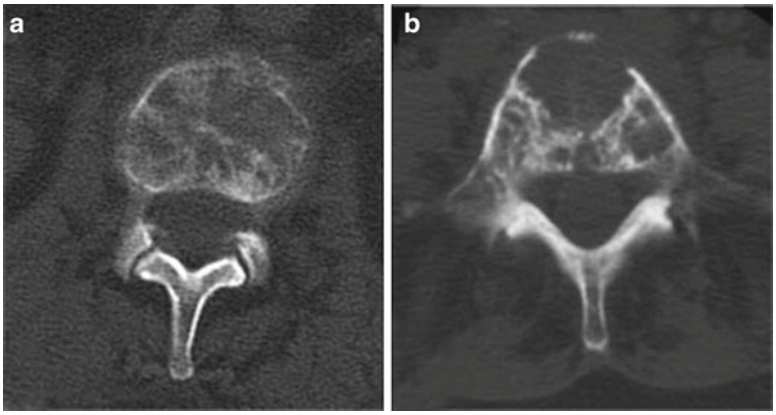

Fig. 2.2 Typical mixed bone lesions in the second (**a**) and fifth (**b**) lumbar vertebrae, due to metastatic breast carcinoma in two separate patients (The above figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

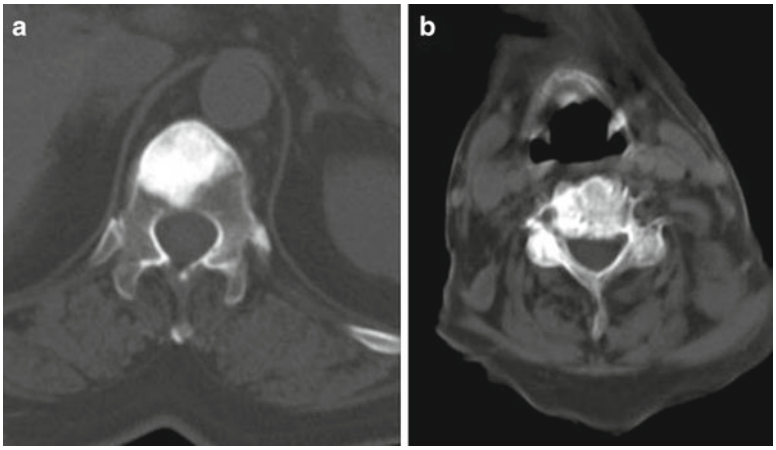

Fig. 2.3 Osteosclerotic bone metastases in two different breast cancer patients, in the eighth thoracic (**a**) and fourth cervical (**b**) vertebrae (This figure is reprinted from Clinical and Experimental Metastasis Journal, Vol 24: 49–56, table 1, copyright 2007, with kind permission of Springer Science+Business Media B)

statistically significant correlation with pain and a strong, positive, statistically significant correlation with QOL (partial correlation coefficients −0.57 and 0.64 respectively) (Table 2.4). These results showed that there is a clear correlation between the clinical status of patients and the type of bone metastases and that the level of bone resorption at sites of bone metastasis is a major determinant of the level of morbidity and suffering [35]. A link between pain and the level of resorption in patients with metastatic bone disease has also been demonstrated in other studies [37].

Table 2.3 Summary of results of clinical and radiological evaluations

	Pts with lytic bone lesions (n = 32)	Pts with mixed bone lesions (n = 30)	Pts with sclerotic bone lesions (n = 18)	p value
Pain score (0–10)	8.1 ± 2.2	6.6 ± 1.7	4.6 ± 1.3	<0.05[a]
Quality of life (0–100)	31.4 ± 14.6	45 ± 10.9	61.1 ± 15.5	<0.05[a]
Performance status (0–100)	58.6 ± 9.7	64.6 ± 7.3	66.6 ± 10	<0.05[a]
Bone density: (Hounsfield units)	116.3 ± 40.4	240.7 ± 69.4	444 ± 86.6	<0.05[a]
Opioid consumption: (%)	100 %	86.6 %	55.5 %	<0.05[b]

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Data presented as mean values ± standard deviation
Pts patients
[a]ANCOVA test: All pair wise comparisons between groups were statistically significant, apart from performance status between the mixed and sclerotic groups
[b]X^2 test, followed by the Holm's sequential Bonferroni method

Table 2.4 Partial correlation coefficients between pain score, quality of life, performance status and bone density

Variables	Bone density	Pain	Quality of life
Pain	−0.57[a]	–	–
Quality of life	0.64[a]	−0.78[a]	–
Performance status	0.39[a]	−0.51[a]	0.49[a]

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[a]Statistically significant after controlling for type I error

The location of bone metastases is another determinant of the clinical picture and level of suffering. Patients with vertebral metastases typically present with neck or back pain that may be exacerbated by palpation or local application of pressure or movement. Ten percent of such patients suffer from pain due to spinal instability. In such cases pain may be excruciating, worsening upon patient movement. Base of skull involvement can result in nerve palsies, neuralgias or headache [7]. Finally, hip or femoral metastases commonly cause back or lower limb pain [7] and are associated with marked movement impairment.

Bone metastases are frequently complicated by pathologic fractures and are the second most common cause of such fractures after osteoporosis. Pathologic fractures are a result of bone destruction at metastatic bone sites and are most commonly seen in osteolytic metastases involving the cortex. Bone lysis and the loss of structural integrity at metastatic sites inevitably lead to a reduction of the loading capabilities of the affected bone and ultimately to fracture. Rib fractures and

vertebral collapses are especially frequent [7], but the most detrimental fracture in terms of patient's QOL and performance status are the fractures of weight bearing long bones. Such fractures occur in 10–20 % of patients with metastases to bone [25] and the most commonly affected site is the proximal femur [38].

Many authors have tried to investigate and reveal the risk factors for pathologic fractures. A number of studies have reported that such fractures appear in patients with lesions that exceed 50 % of the diameter of the affected bone [39, 40]. Other studies have shown that lesions >2.5 cm are at greater risk to fracture as compared to metastatic lesions ≤2.5 cm [41]. Bertin and co-workers have also shown that avulsion of the lesser trochanter is another important risk factor for pathologic fractures in the femur [42]. A set of criteria have been proposed for prophylactic internal fixation in patients with peritrochanteric femoral lesions. These criteria are as follows: (a) lesion size >2.5 cm (b) lesion diameter greater than 50 % of the diameter of the affected bone and (c) avulsion of the lesser trochanter [43].

Mirels H has proposed a scoring system for impending pathologic fractures of long bones that is in our opinion very useful. The system incorporates variables such as size of lesion, radiographic appearance, level of suffering (pain), and location of metastasis. Through the assessment of patients, each variable is assigned a score. It was shown that lesions that scored greater than seven points generally required internal fixation and lesions with scores equal or greater than ten had an estimated risk to fracture greater than 50 % [44].

The probability of undergoing a pathologic fracture increases with the duration of metastatic bone disease and this complication is more common in patients with metastases confined to bone. This is rather paradoxical since such patients have a relatively good prognosis as compared to patients with extraosseus metastases [1, 13]. Special attention should be given to the evaluation of patients with impending pathologic fractures in order to prevent this severe complication. Risk factors should be carefully evaluated and patients at risk should be referred to orthopedic surgeons for prophylactic surgery. This need is of uttermost importance if we take into consideration that it was recently reported that pathologic fractures not only deteriorate the QOL of patients, but also correlate with a reduced survival [45].

Bone marrow infiltration by tumor cells is favored by the high blood flow in the red marrow [46], the adhesive molecules of tumor cells that bind them to marrow stromal cells and bone matrix [47] and the large repository of immobilized growth factors that are released during the process of bone resorption [48]. Such factors serve as a fertile ground for tumor cell growth and proliferation [47]. However not all patients with bone marrow infiltration develop bone metastases. It has been shown that 25 % of breast cancer patients were found to have tumor cells in their bone marrow prior to surgery. After a median follow up of 76 months only 48 % of these patients developed bone metastases. Metastatic bone disease was also diagnosed in 25 % of patients who were free of bone marrow tumor cell infiltration prior to surgery [48, 49]. Bone marrow infiltration and tumor growth into the marrow space is in most cases accompanied by extensive fibrosis and may result in reduced haemopoiesis and pain. Useful diagnostic signs are leukoerythroblastosis with immature white and red cells in peripheral blood smears. This is seen in about 50 %

of patients with bone marrow infiltration and is a result of extramedullary haemopoiesis [33]. Early detection of bone marrow metastases enables earlier therapy [50] that may result in alleviation of pain [51] and prevention of complications of metastatic bone disease [52, 53]. Both magnetic resonance imaging (MRI) and bone marrow scintigraphy have proved to be effective in detecting bone marrow involvement, MRI being superior in terms of sensitivity and specificity [54].

Spinal cord compression is a medical emergency that calls for an urgent evaluation and treatment [7], since neurological recovery is probable only in the case that compression is relieved within 24–48 h from the time of diagnosis [55]. This complication generally occurs late in the natural history of cancer and is considered as a pre-terminal event since upon its occurrence prognosis is rather poor. The thoracic spine is most commonly affected.

Local pain and tenderness over the affected cord lesion is the commonest initial symptom in patients with spinal cord compression due to metastatic bone disease and usually precedes neurological manifestations by weeks or months. Pain is more intense with activities such as coughing or straining that increase intradural pressure and may worsen at night time [7]. Metastases with a more lateral localization involving nerve roots bring about radiculopathy with focally sited segmental pain, dermatomal sensory disturbances such as numbness and tingling and weakness in muscles innervated by the affected root. At diagnosis of spinal cord compression, patients typically present with leg weakness. In most cases both sensory and motor loss is seen and defects of both power and sensation occur at and below the involved level. Sphincter or bladder function loss occurs late and is associated with poor prognosis. Vertebral metastases below the L1 or L2 level may produce the cauda equina syndrome that involves bladder or bowel dysfunction (retention or incontinence), severe low back pain with motor weakness, sensory loss or pain in one or more commonly both legs, saddle anesthesia and sexual dysfunction. In a retrospective study by Hill ME et al. that involved 70 patients with spinal cord compression secondary to breast cancer, it was found that at the time to diagnosis all patients had radiological evidence of bone metastases and the most common symptoms were motor weakness (96 %), followed by pain (94 %), and sensory (79 %) or sphincter (61 %) disturbances. The majority of patients (91 %) had at least one symptom for more than a week prior to diagnosis [56].

A detailed history taking and physical and neurological examination is critical for diagnosing spinal cord compression in cancer patients. Any patient with a history of cancer and back pain should be investigated for spinal cord compression. In a prospective study involving cancer patients it was shown that there was a 30 % probability of spinal cord compression at the presence of any of the following risk factors: back pain, abnormal neurological findings at neurological examination, or detection of vertebral metastases through radiologic assessment (plain x-rays). In the case that two of the above factors were present, the likelihood of spinal cord compression was between 60 % and 70 % and in the presence of all three factors the probability was greater than 90 % [57].

MRI is very useful in the evaluation of possible malignant cord compression providing detailed information on the extent and the number of epidural

compressions [58, 59]. Patients are generally managed with either decompressive surgery or radiotherapy or a combination of the two therapeutic modalities. Surgery is usually reserved for younger patients with a good performance status, patients with a single site of cord compression and in cases of fracture dislocations and spinal instability [60]. Ambulation is the most important factor for response to therapy prior to treatment and the most important post treatment survival factor [56, 61]. In the study by Hill and co-workers 96 % of patients who were ambulant prior to therapy maintained their ability to walk post therapy and from patients who were unable to walk prior to treatment, only 45 % regained ambulation. The results suggested that that earlier diagnosis and intervention can improve the therapeutic outcome. Additionally, there was no evidence of survival benefit from surgery over radiotherapy as primary treatment [56]. Overall post therapy 20 % of patients improve neurologically, 30 % remain stable and about half of patients deteriorate. The median survival is 7 months for patients who are able to walk post treatment and 1.5 months for non ambulatory patients [62].

2.4 Metabolic Complications: Hypercalcemia of Malignancy

Hypercalcemia is one of the commonest metabolic complications seen in patients with metastatic bone disease, occurring in 3–30 % of cancer patients during the course of their disease [63]. It is most typically seen in patients with lung (squamous cell carcinoma), breast, kidney, ovarian and head and neck tumors [7, 63]. The occurrence of hypercalcemia in breast cancer patients ranges between 30 % and 40 %, but is rather uncommon in patients suffering from colorectal and prostate cancer [63]. This complication is also manifested in patients with hematological malignancies such as multiple myeloma and lymphoma. In multiple myeloma up to a third of patients develop hypercalcemia [64].

Calcium serum concentration is closely regulated by a complex homeostatic mechanism, involving organs such as bone, liver, parathyroid glands, kidneys and gastrointestinal tract. Parathyroid hormone (PTH) has a key role in the whole mechanism. When calcium serum levels are low, PTH is secreted from the parathyroid glands. PTH acts on bone by enhancing osteoclastic resorption with accompanied calcium release and on kidney by reducing urinary calcium excretion and increasing phosphorus excretion. Parathyroid hormone–related peptide (PTHrP) is secreted by a variety of tumors [65, 66] and it has been shown that its actions parallel those of PTH [63, 66]. The level of PTHrP is elevated in up to two thirds of patients with metastatic bone disease and hypercalcemia and in the vast majority of patients with humoral hypercalcemia. It was also demonstrated that impaired hepatic function in women with liver metastases from breast cancer is associated with hypercalcemia [67]. This could be explained by the fact that impaired hepatic function may result in a reduced PTHrP metabolism and consequently enhanced bone resorption. Increased calcium serum level also interferes with the action of anti-diuretic

hormone (ADH) at the distal nephrone, causing polyuria and polydipsia, a syndrome like diabetes insipitus. This results in dehydration that further exacerbates hypercalcemia [63].

Three distinct syndromes have been described in hypercalcemia of malignancy: (a) the humoral hypercalcemia of malignancy, (b) hypercalcemia associated with skeletal metastases, and (c) hypercalcemia accompanying hematological malignancies. Humoral hypercalcemia of malignancy (HHM) is manifested in patients with elevated serum calcium in the absence of skeletal metastases. The syndrome is a result of circulating PTHrP released from the tumor itself. In patients with evidence of osteolysis produced by tumor cells, metastases in bone stimulate bone resorption by the local release of PTHrP. During the process of bone resorption local factors such as the transforming growth factor alpha (TGF-a), TGF-b, epidermal growth factor and interleukin 1 are released, promoting the secretion of PTHrP from tumor cells [68, 69]. A viscous cycle is therefore formed enhancing bone resorption and calcium release. There is evidence for a humoral contribution in this syndrome, since in breast cancer patients the extent of metastatic bone disease does not correlate with the level of hypercalcemia [70]. The third syndrome is the one in which hypercalcemia is manifested in patients with hematological malignancies. Hypercalcemia is rather uncommon in patients with Hodgkins and non-Hodgkins lymphoma, but as mentioned before it occurs in about one third of multiple myeloma patients [64]. In a study with 165 patients admitted to a Hematology Department, hypercalcemia was documented in nine patients with myeloma, in five patients with high grade B-cell non-Hodgkins lymphoma and in one with myeloid neoplasia [71]. In the cases with B-cell non-Hodgkins lymphoma circulating levels of PTHrP were detected [71] and the same was true for one third of patients with elevated calcium serum level and multiple myeloma [71]. The above findings indicate that PTHrP mediated hypercalcemia is not only seen in patients with solid tumors, but also in patients with hematological malignancies.

The clinical picture of patients with hypercalcemia is in many cases nonspecific and clinicians should have a high index of suspicion. Asymptomatic patients turn out to have fatigue and malaise or signs of hypertension or renal failure. In symptomatic patients common symptoms are polyuria, polydipsia, anorexia, nausea, vomiting, constipation and bone pain. Patients may also present with abdominal pain (due to peptic ulcer or pancreatitis) or loin/ureteric pain due to urinary tract stones. Mental disturbances include confusion, depression, psychosis, alteration of the level of consciousness and in severe cases comma. In case that hypercalcemia is not corrected, renal function and mental status deteriorate and death may result from renal failure and cardiac arrhythmias. Symptoms and signs of hypercalcemia are presented in Table 2.5.

The prognosis of hypercalcemic patients is poor and treatment is effective in improving the symptomatology but not in prolonging survival [63]. Patient rehydration, bisphosphonates [72, 73], calcitonin [74], and diuretics such as frusemide [75] are important in the overall management of symptomatic hypercalcemia that is a metabolic emergency and calls for immediate patient evaluation and treatment.

Table 2.5 Clinical features and symptoms in patients with hypercalcemia

Non specific symptoms
Malaise
Fatigue
Gastrointestinal
Nausea and vomiting
Anorexia
Constipation
Abdominal pain
Mental disturbances
Confusion
Depression
Psychosis
Drowsiness
Apathy
Coma
Renal
Polyuria
Polydipsia
Signs of dehydration
Ureteric or loin pain

2.5 Symptom Clusters in Cancer Patients with Bone Metastases

Studies in cancer symptom research have mainly focused on the management and severity of individual symptoms [76]. This approach has helped advance our understanding of a particular symptom. However, symptoms seldom occur in isolation in patients with advanced cancer. It is therefore important to focus on evaluating multiple symptoms, using cross-sectional and longitudinal study designs. The term "symptom cluster" was first quoted by Dodd et al. [77] in their research with pain, fatigue, and sleep disturbances. They defined symptom clusters as three or more concurrent symptoms that are related to each other, which may or may not have the same etiology. A subsequent paper published in 2005 described symptom clusters as two or more symptoms that are related to each other, occur together, are a stable group and are relatively independent of other clusters [78]. The relationship, strength and time frame needed for these clusters to present have not been specified. Symptom clusters may have an adverse effect on patient outcomes and a synergistic effect as a predictor of patient morbidity.

Palliative radiotherapy has been well established for the treatment of symptomatic bone metastases. Although pain might have improved, patients in some clinical trials reported no significant improvement in quality of life (QOL). Failure to improve QOL significantly after palliative radiotherapy can be due to multiple bone metastases in patients. Pain relief in one irradiated site may unmask pain in other bony metastatic sites. It is important to explore whether bone pain "clusters" with other

common symptoms in advanced cancer. There is suggestion that pain, depression, and fatigue may occur in combination. Failure to recognize these symptom clusters may result in failure to improve overall QOL. One study conducted at an outpatient palliative radiotherapy clinic asked patients with bone metastases, during their initial consultation, to rate their symptom distress using the Edmonton Symptom Assessment Scale (ESAS) with an 11-point categorical scale (0–10; 0 = absence of symptom and 10 = worst possible symptom) [78, 79]. The ESAS evaluates nine symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, sense of well-being, shortness of breath and has been successfully validated in cancer patients [79, 80]. Patients were asked to rate the item "pain" in the ESAS as bone pain at the irradiated site. All primary assessments and questionnaires were completed prior to radiation simulation and at weeks 1, 2, 4, 8, and 12 post-radiation, ESAS scores were obtained by telephone interview. Responders to radiation treatment were assigned as having complete or partial response, as defined by the International Bone Metastases Consensus Working Party [81]. Between January 1999 and January 2002, 518 patients (280 male and 238 female) with bone metastases provided complete baseline data on ESAS at the time of consultation.

Three clusters were identified and accounted for 66 % of the total variance at baseline. Cluster one included fatigue, pain, drowsiness and poor sense of well being and accounted for 44 % of the total variance. Cluster 2 included anxiety and depression and accounted for 12 % of the total variance. Cluster 3 included shortness of breath, nausea and poor appetite and accounted for 10 % of the total variance [82]. In comparing the pattern of symptom cluster dynamics in the responders, pain clustered out in weeks 8 and 12; breathlessness clustered out in week 2. Only two symptom clusters remained in weeks 2, 8, and 12. In non-responders, symptom clusters prevailed in all weeks, except for week 8 with breathlessness clustering out. Over time, symptom components of the symptom clusters changed after radiation treatment. However, some symptoms often appeared in the same cluster. Fatigue and drowsiness remained together for all weeks in both groups; anxiety and depression also followed each other. Overall, it was shown that radiotherapy did indeed influence the structure of symptom clusters in both the responders and non-responders. It appears that pain clustered with fatigue, drowsiness and poor sense of well being at baseline [82]. For the opioid consumption in responders and non-responders through weeks 1–12, there is an obvious difference between the mean morphine equivalency of opioid consumption between the two groups. Non-responders to treatment had a higher intake of analgesics than responders. Analgesic consumption in responders decreased.

As cancer patients experience a wide range of symptoms that may not have been captured by ESAS, it is important for similar, comprehensive assessment tools to be used in all symptom cluster research. A sub-analysis of patients reporting exclusively non-zero ESAS scores at baseline was undertaken from this same data set by Chen et al. in order to try and identify symptom clusters in this subgroup of patients and to compare clusters with those identified in the total population [79]. The secondary objective of this study attempted to establish whether symptom clusters in bone metastases patients varied when extracted using different statistical

methods. A data set compiled from patients with bone metastases identified a non-zero subgroup of patients who reported severity scores > 0 for all nine ESAS symptoms at baseline. Principal Component Analysis (PCA), Hierarchical Cluster Analysis (HCA) and Exploratory Factor Analysis (EFA) were performed to derive symptom clusters at baseline, 1, 2, 4, 8 and 12 weeks after radiation therapy (RT) for the non-zero subgroup. Both EFA and HCA effectively capture the essence of symptom cluster as a grouping of concurrent and related symptoms. EFA is unique in that it functions on the assumption that symptoms in a cluster share a common underlying latent factor which binds two or more symptoms together. HCA classifies and tries to put similar entities together into a cluster and attempts to separate this cluster from other clusters [83]. It was found that different symptom clusters were recognized in the non-zero subgroup compared with the total patient population, regardless of statistical method utilized. Symptom cluster results varied depending on statistical method employed for analysis. This sub-analysis did not provide a complete consensus between all three methods. Anxiety and depression were the only two ESAS symptoms to consistently occur in the same cluster across different methods over time. This study then concluded that the quantity and composition of symptom clusters varied based on whether patients with zero symptom severity scores were included at baseline as well as which statistical analysis method was employed.

A study by Hadi et al. explored how patients' worst pain clustered together with functional interference items as assessed by the Brief Pain Inventory (BPI), as well as determining whether symptom clusters change with palliative radiotherapy in responders and non-responders to radiation[84]. The BPI is a multidimensional assessment tool often used in oncology as a multiple item measure of pain, measuring both its' sensory and affective dimensions [85]. A total of 348 outpatients provided their scores of worst pain at site of radiation treatment and functional interference at baseline, 4, 8 and 12 weeks post radiation therapy. Interrelationships between symptoms were determined at all time points by using PCA on each of the worst pain scores and seven functional interference items in responders and non-responders. Changes in worst pain have shown to correlate significantly with six of seven life functions [86]. Two clusters were identified at baseline and accounted for 67 % of the total variance. Cluster 1 accounted for 55.6 % of the total variance and was comprised of general activity, walking ability, normal work, enjoyment of life and worst pain. Cluster 2 accounted for 11.4 % of the total variance and included mood, sleep and relations with others. Cronbach alpha co-efficient demonstrated good internal consistency. This study served to reaffirm the importance of achieving pain reduction as a treatment goal for palliative radiotherapy in cancer patients [87].

A reanalysis of symptom clusters comparing different statistical methods in patients with bone metastases was reported by Chen et al. [85]. The same cohort of 348 outpatients as analyzed by Hadi et al. was utilized for secondary analysis [84]. The data set compiled using the Brief Pain Inventory was analyzed using the HCA and EFA in order to identify symptom clusters at baseline, 1, 2 and 3 months following radiation treatment. These clusters were then compared to the clusters derived via PCA in the Hadi et al. paper [84]. Using PCA, HCA and EFA, the further separated subgroups of responders and non-responders to radiation therapy (RT) identified

symptom clusters as experienced by each subgroup at same time points. The three statistical methods used provided little correlation and did not provide absolute consensus at any time point in this study. There were varying patterns of symptom cluster presentation among both subgroups over time regardless of analytical method utilized. The core cluster of symptoms including worst pain, walking ability, general activity, normal work and life enjoyment often presented in the same cluster. This reanalysis concluded that the presence and constitution of symptom clusters varied depending on the statistical method employed, thus necessitating the use of a common method to help attain consistency in symptom cluster research.

In conclusion, it is important for health care professionals to take a detailed history of the commonly encountered symptoms in cancer patients with bone metastases. Various symptom assessment tools are available for use in order to enable data collection to help analyze and thus identify symptom clusters. The therapeutic importance of symptom clustering in bone metastases patients necessitates further study. Researchers should recognize the most clinically meaningful statistical findings when considering the optimal method for identifying useful symptom clusters in order to provide the best insight for symptom management for bone metastases patients [84].

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