

Skeletal Complications of Malignancy

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The skeleton is the most common organ to be affected by metastatic cancer, and tumors arising from the breast, prostate, thyroid, lung, and kidney possess a special propensity to spread to bone. Breast carcinoma, the most prevalent malignancy, causes the greatest morbidity. Of great clinical importance is the observation that metastatic bone disease may remain confined to the skeleton. In these patients, the decline in quality of life and eventual death is due almost entirely to skeletal complications and their subsequent treatment. Bone pain is the most common complication of metastatic bone disease, resulting from structural damage, periosteal irritation, and nerve entrapment. Recent evidence suggests that pain caused by bone metastasis may also be related to the rate of bone resorption. Hypercalcaemia occurs in 5–10% of all patients with advanced cancer but is most common in patients with breast carcinoma, multiple myeloma, and squamous carcinomas of the lung and other primary sites. Pathologic fractures are a relatively late complication of bone involvement. The clinical courses of breast and prostate carcinoma are relatively long, with a median survival of 2–3 years. For patients with breast carcinoma, good prognostic factors for survival after the development of bone metastases are good histologic grade, positive estrogen receptor status, bone disease at initial presentation, a long disease free interval, and increasing age. In addition, patients with disease that remains confined to the skeleton have a better prognosis than those with subsequent visceral involvement. For patients with prostate carcinoma, adverse prognostic features include poor performance status, involvement of the appendicular skeleton and visceral involvement, whereas for patients with multiple myeloma, the levels of serum β_2 -microglobulin and lactate dehydrogenase and the immunologic phenotype are the most important factors. These prognostic factors may be useful in planning the rational use of bisphosphonates in the treatment of advanced cancer. *Cancer* 1997;80:1588–94.

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The skeleton is the most common organ to be affected by metastatic cancer. Bone metastases from carcinomas of the breast, lung, prostate, kidney, and thyroid are most frequent¹ (Table 1). The prevalence of skeletal disease is greatest in breast and prostate carcinoma, reflecting both the high incidence and the relatively long clinical courses of these tumors. These two cancers probably account for more than 80% of cases of metastatic bone disease. In breast carcinoma, the incidence of bone metastases has been found to be significantly higher in association with tumors that produce parathyroid hormone-related peptide (PTHrP)² and are either steroid receptor positive³ or well differentiated,⁴ whereas in prostate carcinoma, bone metastases are more often associated with poorly differentiated tumors.⁵

Distribution of Bone Metastases

Although the variability in metastatic patterns is undoubtedly influenced by molecular and cellular biologic characteristics of both the tumor cells and the tissues to which they metastasize, other factors,

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TABLE 1
Incidence and Prognosis of Bone Metastases^a

	Incidence of advanced disease	Median survival (mos)	5-yr survival
Myeloma	95–100%	20	10%
Breast	65–75%	24	20%
Prostate	65–75%	40	25%
Lung	30–40%	<6	<5%
Kidney	20–25%	6	10%
Thyroid	60%	48	40%
Melanoma	14–45%	<6	<5%

^a Data from Rubens and Coleman.¹

including vascular pathways and blood flow, are also important. Bone metastases most commonly affect the axial skeleton. This is where the red marrow is situated in adults, and this pattern of distribution suggests that physical properties of the circulation within the bone marrow, including capillary structure and sluggish blood flow, could assist in the development of bone metastases. In addition, the high incidence of bone metastases without corresponding lesions in the lung suggests that an alternative pathway of spread to the pulmonary circulation may be relevant. Fifty years ago, Batson showed in elegant cadaver experiments that venous blood in the pelvis and breast flowed not only into the vena cavae, but also into a vertebral-venous plexus of vessels extending from the pelvis throughout the epidural and perivertebral veins and into the thoraco-abdominal wall, head, and neck.⁶ In this low-pressure system, blood is continually subjected to arrest and reversal of the direction of flow as intrathoracic and abdominal pressures change during normal physiologic processes.

Importance of Tumor-Induced Osteolysis

Bone metastases are typically referred to as “lytic,” “sclerotic,” or “mixed,” according to the radiographic appearances of the lesions. Where bone resorption predominates, with little new bone formation, focal bone destruction occurs and the metastases have a lytic appearance. Lytic metastases are most common in multiple myeloma, melanoma, and breast, lung, thyroid, renal, and gastrointestinal malignancies. Conversely, in bone metastases characterized by increased osteoblastic activity, the lesions appear sclerotic. Metastases from prostate carcinoma especially, but also those from breast, lung, carcinoid, and medulloblastoma tumors, give rise to sclerotic lesions. However, this classification is simplistic, and both processes are typically accelerated in the affected bone. This acceler-

ation may be evident in a number of ways: on radiographs of the appropriately termed “mixed” lesions; histologically, with evidence of increased osteoclast activity and resorption cavities even within sclerotic lesions;⁷ and, as has been demonstrated most recently, on biochemical evaluation.⁸

The development of specific biochemical markers of bone metabolism has allowed objective assessment of the general effects of cancer on bone cell function. Table 2 shows the urinary excretion of a variety of bone resorption markers in patients with breast, prostate, and other solid tumors affecting bone who participated in a clinical trial.⁹ The data are expressed as a ratio of the mean value in patients to the mean value in age- and gender-matched controls. With the exception of calcium excretion, which is known to be an inaccurate marker of the rate of bone resorption, all three groups of patients had evidence of increased bone resorption irrespective of the radiologic appearances of the disease. These results indicate that bone resorption in prostate carcinoma is important despite the sclerotic nature of most prostate carcinoma metastases, with values of resorption markers at least as high as those noted for breast carcinoma and other solid tumors.

Prognosis and Clinical Course

With the possible exception of PTHrP in breast carcinoma, there are no especially powerful predictors for identifying patients who are at particularly high risk of developing bone metastases; this makes it difficult to design clinical trials to assess the prevention of bone metastases. In a study of 2240 consecutive patients presenting to a single center over a 10-year period with localized breast carcinoma, 30% had relapsed after a median follow-up of 5 years, and in 184 (8%) the first site of metastasis was in bone.⁴ Although bone was the most common first site of distant spread (in 47%

TABLE 2
Biochemical Evidence of Increased Bone Resorption in Solid Tumors^a

	Breast (n = 29)	Prostate (n = 10)	Other (n = 7)
Ntx	2.55	7.61	3.19
Crosslaps	1.84	4.93	2.86
Free Dpd	2.22	3.19	2.47
Hydroxyproline	1.66	2.92	2.27
Urinary calcium	0.78	1.77	2.46

^a Data are expressed as ratios of the mean value in patients to the mean value in age- and gender-matched controls. NTX: N-terminal telopeptide of type I collagen. Dpd: deoxypyridinoline.

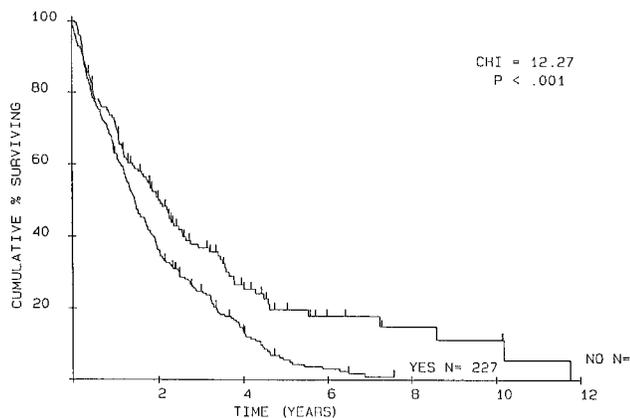


FIGURE 1. Survival after first recurrence in the skeleton is shown, according to subsequent development of nonosseous metastases or disease confined to the skeleton. Yes: bone and other subsequent sites; no: bone only.

of patients), this study indicated that the annual incidence of first recurrence in bone from an unselected population of breast carcinoma patients is only approximately 1–3%.

The median survival after the first recurrence of breast carcinoma in bone is 20 months.⁴ This is in marked contrast to the survival of those with first recurrences of breast carcinoma in the liver (3 months) or with bone metastases from nonsmall cell lung carcinoma (3–6 months). Figure 1 shows that the probability of survival for patients with bone metastases from advanced breast carcinoma is influenced by the subsequent development of metastases at extraosseous sites. In a recent study of 367 patients with bone metastases, those with additional organ involvement had a median survival of 1.6 years, compared with 2.1 years for those with disease remaining clinically confined to the skeleton ($P = <0.001$).¹⁰ A number of factors predict for the likelihood of disease to remain confined to the skeleton (Table 3). Patients with disease confined to bone are more likely at diagnosis to be older, postmeno-

pausal women with lobular carcinoma and are less likely to have poorly differentiated, ductal Grade 3 tumors. Patients with disease confined to bone are also more likely to have presented initially with little or no involvement of axillary lymph nodes.

In prostate carcinoma, the clinical course is also relatively long; in men with good performance status and disease confined to bone that affects the axial skeleton, the median duration of disease control by androgen blockade is 4 years.¹¹ For these patients, the median survival is 53 months, compared with 30 months for those with additional visceral disease and only 12 months for patients with poor performance status and both bone and visceral disease. Table 4 shows the most important prognostic factors for advanced prostate carcinoma, multiple myeloma, and breast carcinoma.^{1,12,13}

For patients with multiple myeloma, the median survival is 2–3 years, with a probability of surviving 5 years of approximately 15–25%. There are many prognostic factors in myeloma; serum β_2 -microglobulin and C-reactive protein (CRP) are probably the most useful independent factors. The median duration of survival is only 6 months for patients with high levels of β_2 -microglobulin and CRP, compared with 54 months for those with low levels.¹⁴

The effect of various clinical, tumor, and biologic characteristics on the probability of survival after the development of bone metastases from breast carcinoma has been assessed with the Cox proportional hazards model.¹⁰ Patients who had bone disease coincident with the initial presentation of their breast carcinoma had better survival than other patients. Histologic grade and type were the next most significant prognostic factors, with Grade 1 and 2 ductal or lobular carcinomas having the best and Grade 3 the worst prognosis. Estrogen receptor positivity, a long disease free interval (≥ 3 years vs. < 3 years), and premenopausal status were other good prognostic factors (Table 5).

TABLE 3
Evolution of Bone Metastases in Breast Carcinoma, Showing Factors That Predict for Disease Remaining Confined to the Skeleton^a

	Bone only (n = 139)	Bone + other sites (n = 228)	P value
Postmenopausal	63%	43%	0.0002
Lymph node negative	29%	18%	0.02
Lobular	21%	12%	0.04
Premenopausal	24%	37%	0.009
<4 lymph nodes positive	16%	30%	0.001
Grade 3	19%	32%	0.001

^a Data from Coleman et al.¹⁰

TABLE 4
Well-Established Prognostic Factors in Metastatic Bone Disease^a

Prostate	Myeloma	Breast
Skeletal distribution	β_2 -microglobulin	Extrasosseous disease
Performance status	Proliferative activity	Disease free interval
Extrasosseous disease	C-reactive protein	Performance status
Alkaline phosphatase	Immunologic phenotype	Estrogen receptor status
Hemoglobin	LDH	Age
PSA fall	Serum creatinine	Histologic grade
	Hypercalcemia	

PSA: prostate specific antigen; LDH: lactate dehydrogenase.

^a Data from Coleman et al.,¹⁰ Eisenberger et al.,¹² and Kyle and Blade.¹³

Skeletal Complications

Bone metastases cause considerable morbidity. This includes pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow infiltration. In two large randomized trials involving breast carcinoma¹⁵ and multiple myeloma¹⁶ patients who received chemotherapy, the mean skeletal morbidity rates (the number of skeletal events per year) in the absence of bisphosphonates were 3.5 and 2.0, respectively.

Looking in more detail, first at a study of 498 patients with first relapse in bone from breast carcinoma, 145 (29%) developed 1 or more major complications of metastatic bone destruction. Hypercalcemia occurred in 86 (17%), pathologic fracture in 78 (16%), and spinal cord compression in 13 (3%). Similar results were identified in a more recent report from the same institution (Table 6).¹⁰ In multiple myeloma, the prevalence of skeletal complications at diagnosis was assessed in 254 patients.¹⁷ Bone pain was reported by 75%. This was in the back in 50%, the ribs in 20%, the upper limbs, in 7%, and the lower limbs in 11%. Radiographic evaluation revealed the presence of ver-

tebral fracture in 54%, and 33% had hypercalcemia at diagnosis.

Hypercalcemia

Hypercalcemia is probably the most common metabolic complication of malignant disease and is clinically important because of the morbidity associated with it. If left untreated, moderate-to-severe hypercalcemia (serum calcium >3.0 mmol/L) causes a number of unpleasant side effects related to dysfunction of the gastrointestinal tract, kidneys, and central nervous system. With even greater elevations in serum calcium, renal function and level of consciousness deteriorate, and death ultimately ensues as the result of cardiac arrhythmias and acute renal failure.

Although there are many similarities between the biochemical features of humoral hypercalcemia of malignancy and hyperparathyroidism, these disorders are seldom mistaken for one another in clinical practice. Patients with cancer-related hypercalcemia almost invariably have clinically advanced tumors by the time hypercalcemia has developed; thus, the diagnosis of hypercalcemia of malignancy is usually appar-

TABLE 5
Multivariate Analysis of Prognostic Variables in Bone Metastasis from Breast Carcinoma, as Assessed with the Cox Proportional Hazards Model^a

Variable ^b	P value	RR	95% CI
Age (<70 vs. ≥70)	0.006	1.67	0.2-2.4
Menopausal status (pre vs. post)	0.02	1.36	0.1-1.8
Histology ^c (ductal grade)	<0.0001	1.75	1.4-2.2
ER status (positive vs. negative)	<0.0001	1.99	1.5-2.7
DFI (≥3 years vs. <3 years)	0.002	1.62	1.2-2.2
Bone disease at presentation (yes vs. no)	<0.0001	2.65	1.7-4.0
Stage at presentation (I/II vs. III/IV)	0.02	1.40	1.1-1.9

RR: relative risk; CI: confidence interval; DFI: disease free interval; ER: estrogen receptor.

^a Data from Coleman et al.¹⁰

^b The group listed first had better survival.

^c Nonductal histologies are included with ductal Grade 2. Ductal grade is 1, 2, or 3. Grades 1 and 2 are compared with 2 and 3. To compare 1 with 3 would be RR.

TABLE 6
Frequency of Major Complications of Skeletal Involvement^a

Complication	No. (%) of patients
Hypercalcemia of malignancy	70 (19%)
Pathologic feature of a long bone	68 (19%)
Spinal cord compression	36 (10%)
Bone marrow failure/leukoerythroblastic anemia	33 (9%)

^a Data from Coleman et al.¹⁰

ent at the bedside or with the aid of a few simple screening investigations. Regrettably, however, physicians not trained in the treatment and support of cancer patients regularly mistake the symptoms of malignant hypercalcemia for those of cancer and/or its treatment.

Hypercalcemia is not distributed evenly in the cancer population and occurs most often in those with squamous cell carcinoma of the lung, adenocarcinoma of the breast and kidney, and certain hematologic malignancies (particularly multiple myeloma and lymphoma). In most cases, hypercalcemic cancer patients have increased osteoclastic bone resorption, either multifocally (as in the case of myeloma or metastatic breast carcinoma) or as a generalized process, stimulated by PTHrP and other tumor products. While often associated with metastatic bone disease, many instances of cancer-related hypercalcemia are due to the systemic release of these bone-resorbing humoral factors rather than local bone dissolution.¹⁸

Local osteolytic hypercalcemia results in excessive focal hydroxyapatite and calcium release by tumor metastases. One or more of the prostaglandins, growth

factors that stimulate prostaglandin function, and cytokines (particularly interleukins, lymphotoxin, and tumor necrosis factors) appear to be involved in local osteoclast activation, although the precise contribution of each factor remains to be defined. Other mechanisms underlying hypercalcemia include impaired renal perfusion due to dehydration; calcium is a potent diuretic, causing salt and water loss and depletion of the intravascular space. In addition, in myeloma, renal impairment may also result from the deposition of Bence Jones proteins. Finally, some lymphomas produce active metabolites of vitamin D, which may cause hypercalcemia through increased bone resorption and intestinal absorption of calcium.

Pathologic Fracture

Metastatic destruction of bone reduces its load-bearing capabilities, resulting initially in trabecular disruption and microfractures and subsequently in total loss of bony integrity. Rib fractures and vertebral collapse are most common, resulting in loss of height, kyphoscoliosis, and a degree of restrictive lung disease. However, the fracture of a long bone or epidural extension of tumor into the spine cause the most disability.

The incidence of pathologic fracture in patients with bone metastases is somewhat uncertain and depends on whether rib and vertebral fractures are also considered. In one series, 150 (8%) of 1800 patients with metastatic bone disease developed a fracture of the femur or humerus; these were secondary to metastases from the breast in 53%, kidney in 11%, lung in 8%, thyroid in 5%, lymphoma in 5%, and prostate in only 3%.¹⁹ In another smaller series of breast carcinoma patients,²⁰ the incidence of

pathologic fractures was 57%, with rib fractures occurring first in 29%, vertebral collapse in 9%, and long bone and pelvic fractures in 9% and 8%, respectively. Vertebral collapse is probably underreported in most series, but Paterson et al., who systematically reviewed serial radiographs in patients participating in a clinical trial of oral clodronate,²¹ showed that a woman with bone metastases from breast carcinoma can on average expect to experience 1.3 vertebral and 0.4 nonvertebral fractures per year.

The probability of developing a pathologic fracture increases with the duration of metastatic involvement and is therefore, somewhat paradoxically, more common in patients with disease confined to bone who have a relatively good prognosis. Because the development of a fracture is so devastating to a 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, and long term administration of bisphosphonates.²²

Spinal Cord Compression

When the development of back pain in a patient with cancer is coincident with an abnormality on a plain spinal radiograph, it should serve as a warning of the possible development of spinal cord compression. In this situation, more than 60% of patients will have myelographic abnormalities²³ or evidence of epidural disease on magnetic resonance imaging.²⁴ The keys to successful rehabilitation are early diagnosis, high dose corticosteroids, and rapid assessment and 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.²⁵

Bone Pain

Bone pain is the most common type of pain from cancer and a significant problem in both hospital and community practice. 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. It is often worse at night, being helped little by sleep and not necessarily relieved by lying down. Pain may occur around joints due to mechanical, chemical, or bony change. There is often disturbance of the highly innervated periosteum, which may give bone pain its neurogenic like qualities and add to its intractability.

Clearly, pain contributes to a patient's quality of life but does not necessarily dominate it. Indeed, the side effects of analgesics may in some situations be

worse than the pain itself, particularly when attention has not been paid to preventing constipation or nausea and the acute effects on alertness and sleep have not been explained to the patient. Well-tolerated, repeatable, effective treatments for bone pain are necessary to try to optimize quality of life for cancer patients. Careful symptomatic and biochemical evaluation has shown that pain and the rate of bone resorption appear to be linked; adequate inhibition of bone resorption appears to be a prerequisite for significant symptomatic improvement after bisphosphonate treatment,²⁶ and recurrence of bone pain after treatment corresponds to an increase in the rate of bone resorption.²⁷

Spinal instability is the cause of back pain in 10% of cancer patients.²⁸ This can cause excruciating pain that is mechanical in origin. The patient is only comfortable when lying still, and any movement produces severe pain. Consequently, the patient may not be able to sit, stand, or walk. Because the pain is mechanical in origin, radiation therapy or systemic treatment will not help; the only solution is stabilization of the spine. This is a major operation with significant morbidity and mortality; but with careful selection of patients, excellent results can be obtained.

Treatment Strategies

It has been estimated at one UK cancer center that the average hospital cost of treating a patient with advanced breast carcinoma is approximately £7600 (1990 costs), with the largest component being hospital bed usage for the complications of metastatic bone disease.²⁹ In another analysis from the United States, hospital costs were on average \$2000 per month (1990 costs), with skeletal disease accounting for 63% of the hospital expenditure.³⁰ With more than 250,000 and 100,000 deaths worldwide each year from breast and prostate carcinoma, respectively, strategies to reduce the incidence of bone metastases or to palliate established skeletal disease are clearly of tremendous clinical importance. As the range of therapeutic possibilities for modifying the clinical course of both the underlying cancer and its effects on bone increase, careful scientific evaluation in the context of randomized clinical trials incorporating economic evaluation is essential. Only through closer collaboration between the research groups and industry can we expect to quantify the clinical utility of these new strategies and target them efficiently to those patients who have the most to gain.

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