# Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity

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**Abstract** The skeleton is the most common organ to be affected by metastatic cancer and the site of disease that produces the greatest morbidity. Skeletal morbidity includes pain that requires radiotherapy, hypercalcemia, pathologic fracture, and spinal cord or nerve root compression. From randomized trials in advanced cancer, it can be seen that one of these major skeletal events occurs on average every 3 to 6 months. Additionally, metastatic disease may remain confined to the skeleton with the decline in quality of life and eventual death almost entirely due to skeletal complications and their treatment. The prognosis of metastatic bone disease is dependent on the primary site, with breast and prostate cancers associated with a survival measured in years compared with lung cancer, where the average survival is only a matter of months. Additionally, the presence of extraosseous disease and the extent and tempo of the bone disease are powerful predictors of outcome. The latter is best estimated by measurement of bone-specific markers, and recent studies have shown a strong correlation between the rate of bone resorption and clinical outcome, both in terms of skeletal morbidity and progression of the underlying disease or death. Our improved understanding of prognostic and predictive factors may enable delivery of a more personalized treatment for the individual patient and a more cost-effective use of health care resources.

## Incidence of Bone Metastases

Bone is the most common site for metastasis in cancer and is of particular clinical importance in breast and prostate cancers because of the prevalence of these diseases. At postmortem examination, ~70% of patients dying of these cancers have evidence of metastatic bone disease (Table 1; ref. 1). However, bone metastases may complicate a wide range of malignancies, resulting in considerable morbidity and complex demands on health care resources. Carcinomas of the thyroid, kidney, and bronchus also commonly give rise to bone metastases, with an incidence at postmortem examination of 30% to 40%. However, tumors of the gastrointestinal tract rarely (<10%) produce bone metastases.

## Distribution of Bone Metastases

Bone metastases most commonly affect the axial skeleton. The axial skeleton contains the red marrow in the adult, which suggests that properties of the circulation, cells, and extracellular matrix within this region could assist in the formation of bone metastases. Evidence exists that blood from some anatomic sites may drain directly into the axial skeleton. In postmortem studies of animals and humans, Batson (2) showed that venous blood from the breasts and pelvis flowed not only into the venae cavae but also into a vertebral-venous plexus of vessels that extended from the pelvis throughout the epidural and perivertebral veins. The drainage of blood to the skeleton via the vertebral-venous plexus may, at least in part, explain the tendency of breast and prostate cancers, as well as those arising in kidney, thyroid, and lung, to produce metastases in the axial skeleton and limb girdles. Of course, the vertebral-venous plexus does not provide the entire explanation of why these cancers metastasize to the skeleton. Molecular and cellular biological characteristics of the tumor cells and the tissues to which they metastasize are of paramount importance and influence the pattern of metastatic spread (3–5).

## Prognosis

In many patients, metastatic bone disease is a chronic condition with an increasing range of specific treatments available to slow the progression of the underlying disease. The survival from the time of diagnosis varies among different tumor types. The median survival time from diagnosis of bone metastases from prostate cancer or breast cancer is measurable in years (4, 6). In contrast, the median survival time from the diagnosis of advanced lung cancer is typically measured in months.

The prognosis after the development of bone metastases in breast cancer is considerably better than that after a recurrence in visceral sites. For example, in a study by Coleman and Rubens (4) of patients whose cancers were diagnosed in the 1970s and 1980s and who were treated at a single institution, the median survival was 24 months in those patients with first

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**Table 1.** Incidence of bone metastases at postmortem examination in different cancers

| Primary tumor | Incidence of bone metastases (%) |
|---|---|
| Breast | 73 |
| Prostate | 68 |
| Thyroid | 42 |
| Kidney | 35 |
| Lung | 36 |
| Gastrointestinal tract | 5 |

NOTE: Data are adapted from Galasko (1) and presented as a table.

recurrence in the skeleton compared with 3 months after first relapse in the liver ($P < 0.00001$).

Coexisting nonosseous metastatic disease is important in determining prognostic differences between patients with bone metastases from the same type of tumor. Additionally, for patients with advanced breast cancer and metastatic disease confined to the skeleton at first relapse, the probability of survival is influenced by the subsequent development of metastases at extraosseous sites. In a study of 367 patients with bone metastases from breast cancer, those who later developed extraosseous disease had a median survival of 1.6 years compared with 2.1 years for those with disease that remained clinically confined to the skeleton (Fig. 1; $P < 0.001$; ref. 7).

## Skeletal Morbidity

***Breast cancer.*** In a study of 718 patients with metastatic breast cancer at a single institution, >50% of women developed skeletal complications (hypercalcemia, spinal cord compression, surgery to bone, radiotherapy to bone, or pathologic fracture; ref. 8). The patients were classified according to the sites of disease at first relapse: 37% had metastatic disease confined to the skeleton, 21% had disease in the skeleton and at other sites, and 42% had no skeletal involvement. Of the women with bone-only disease at first relapse, 81% developed skeletal complications, compared with 60% of women with bone plus extraosseous metastatic disease and 21% of women with no bone metastases at first relapse.

In women with disease confined to the skeleton at first relapse, the median time to first skeletal complication was 11 months, compared with 20 months in women with bone and extraosseous disease and 56 months in women without bone metastases at diagnosis of first relapse. No significant differences occurred between the groups in the type of first skeletal complication. In a multivariate analysis, the most significant predictor of subsequent skeletal complications was the presence of bone metastases at diagnosis of metastatic breast cancer, regardless of other sites of metastatic disease.

A retrospective analysis of 859 patients who developed bone metastases from breast cancer at Guy's Hospital between 1975 and 1991 was done to identify factors that predict complications from skeletal disease (9). Four groups were defined according to the sites of disease at diagnosis of bone metastases: bone disease only ($n = 243$), bone and soft tissue disease ($n = 268$), bone and pleuropulmonary disease ($n = 237$), and bone and liver disease ($n = 111$). Survival from diagnosis of bone metastases was longest for patients with metastatic disease confined to the skeleton (median survival, 24 months; Fig. 2; $P < 0.001$) and was least for patients with concomitant bone and liver metastases (median survival, 5.5 months).

The likelihood of skeletal complications based on the distribution of disease was also assessed in this review of clinical outcomes (ref. 8; Table 2). No differences occurred between the groups of patients in time to pathologic long bone fracture. However, because patients with bone disease confined to the skeleton at diagnosis lived longest, most long-bone fractures occurred in this group. Forty-two long-bone fractures occurred in patients with bone disease only (i.e., one pathologic long-bone fracture in every 5.8 patients) compared with five such fractures in patients with bone and liver disease (i.e., 1 fracture in every 22.2 patients).

Patients with disease confined to the skeleton at diagnosis of bone metastases were more likely to have received radiotherapy to bone than patients with additional extraosseous disease. Eighty-three percent of patients with bone-only disease required radiotherapy for painful skeletal deposits; 60% of these patients required more than one treatment. In contrast, 47% of patients with bone and liver metastases required radiotherapy to bone for pain relief, and only 21% of these required more than one treatment.

***Prostate cancer.*** Prostate cancer is the most prevalent nondermatologic cancer in males. At presentation, ~10% of patients have bone metastases, and almost all patients who die of prostate cancer have skeletal involvement (10). The clinical course of patients with metastatic prostate cancer can be relatively long, and several prognostic factors have been identified, including performance status, tumor grade, hemoglobin, serum lactate dehydrogenase, prostate-specific antigen, and alkaline phosphatase (11–13).

Several studies have attempted to correlate the extent of skeletal metastatic involvement with survival in patients with advanced prostate cancer. A staging system based on

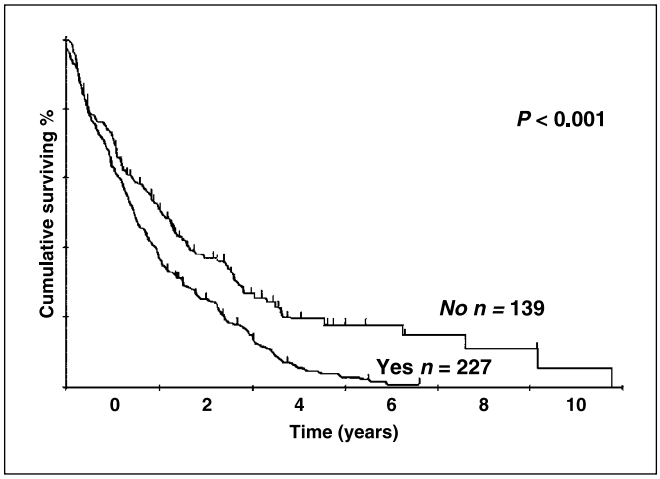


**Fig. 1.** Survival after bone metastases by subsequent development of nonosseous metastases or disease confined to the skeleton. Figure reprinted from Coleman et al. (7).

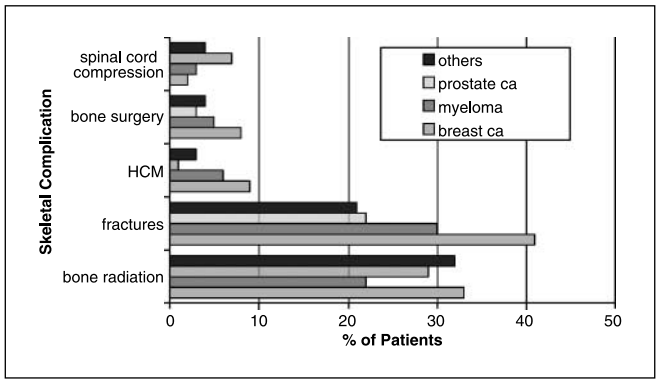


**Fig. 2.** Data were adapted from Coleman (20) and presented as a figure.

distribution of bone metastases according to bone scintigraphy (axial versus appendicular) showed a significant association with survival (14). A different system based on the number of lesions identified by bone scintigraphy was also predictive of survival (15). However, although both systems were able to discriminate between patients at the extremes of their respective scales, neither was particularly effective at discriminating between patients toward the center of the range.

A bone scan index has been developed to quantify the extent of skeletal involvement by tumor more accurately (16). It is based on the known proportional weights of each of the 158 bones derived from the so-called reference man, a standardized skeleton in which postmortem-based individual bone weights were reported for the average adult. The bones were considered individually and assigned a numerical score, representing the percentage involvement with tumor multiplied by the weight of the bone (derived from the reference man). In an analysis of outcomes according to the bone scan index in 191 patients with androgen-independent prostate cancer, patients with low, intermediate, or extensive skeletal involvement had median survivals of 18.3, 15.8, and 8.1 months, respectively (16).

***Other tumors that affect bone.*** Many other solid tumors may affect the skeleton. However, a relatively underevaluated tumor, renal cell cancer has a particular propensity for the development of highly vascular bone metastases that cause severe morbidity (17). This, coupled with the high incidence of hypercalcemia in advanced renal cell cancer, makes the disease particularly relevant for the study of bone-specific treatments and management strategies.

In patients with multiple myeloma, the median survival time is 2 to 3 years, and several prognostic factors have been established (18). For example, the median survival time of patients with high levels of both C-reactive protein and $\beta_2$-microglobulin was 6 months compared with 54 months for patients with low serum levels of these markers (19). Other candidate markers for prognosis include neopterin, interleukin 6, plasma cell labeling index, and lactate dehydrogenase.

## Clinical Features

Skeletal metastatic disease is the cause of considerable morbidity in patients with advanced cancer. The frequency of skeletal complications (also known as skeletal-related events) across a range of tumor types receiving standard systemic treatments but no bisphosphonates is shown in Fig. 2 (20). On average, a patient with metastatic disease will experience a skeletal-related event every 3 to 6 months. However, the occurrence of these morbid events is not regular, with events clustering around periods of progression and becoming more frequent as the disease becomes more extensive and the treatment options reduce.

***Pain.*** Bone metastases are the most common cause of cancer-related pain (21). The pathophysiologic mechanisms of pain in patients with bone metastases are poorly understood but probably include tumor-induced osteolysis, tumor production of growth factors and cytokines, direct infiltration of nerves, stimulation of ion channels, and local tissue production of endothelins and nerve growth factors. Although ~80% of patients with advanced breast cancer develop osteolytic bone metastases, approximately two thirds of such sites are painless (22).

Different sites of bone metastases are associated with distinct clinical pain syndromes. Common sites of metastatic involvement associated with pain are the base of skull (in association with cranial nerve palsies, neuralgias, and headache), vertebral metastases (producing neck and back pain with or without neurologic complications secondary to epidural extension), and pelvic and femoral lesions (producing pain in the back and lower limbs, often associated with mechanical instability and incident pain).

***Hypercalcemia.*** Hypercalcemia most often occurs in those patients with squamous cell lung cancer, breast and kidney cancers, and certain hematologic malignancies (in particular myeloma and lymphoma). In most cases, hypercalcemia is a result of bone destruction, and osteolytic metastases are present in 80% of cases. In breast cancer, an association exists

**Table 2.** Skeletal-related events for patients with breast cancer and bone metastases

| Events | All patients | Bone only ($n$ = 859) | Bone and soft tissue ($n$ = 243) | Bone and visceral ($n$ = 348) |
|---|---|---|---|---|
| Any pathological fracture | 296 (34%) | 128 (53%) | 91 (34%) | 77 (22%) |
| Vertebral fractures | 173 (20%) | 79 (33%) | 47 (18%) | 47 (14%) |
| Long bone fractures | 102 (12%) | 42 (17%) | 37 (14%) | 23 (7%) |
| Fractures at other sites | 108 (13%) | 37 (15%) | 40 (15%) | 31 (9%) |
| Hypercalcemia | 162 (19%) | 62 (25%) | 44 (16%) | 56 (16%) |
| Spinal cord compression | 64 (8%) | 36 (15%) | 15 (6%) | 13 (4%) |

NOTE: Data adapted from ref. 9 and presented as a table.

between hypercalcemia and the presence of liver metastases (23). This association may reflect a relationship between liver involvement and production or reduced metabolism of humoral factors with effects on bone such as parathyroid hormone–related peptide or receptor activator of nuclear factor-κB ligand.

Secretion of humoral and paracrine factors by tumor cells stimulates osteoclast activity and proliferation, and there is a marked increase in markers of bone turnover (24). Several studies have established the role of parathyroid hormone–related peptide in most cases of malignant hypercalcemia (25). The levels of circulating parathyroid hormone–related peptide are elevated in two thirds of patients with bone metastases and hypercalcemia and in almost all patients with humoral hypercalcemia. The kidney also has a role in malignant hypercalcemia; as a result of volume depletion and the action of parathyroid hormone–related peptide, renal tubular reabsorption of calcium is increased, further increasing serum calcium levels.

The signs and symptoms of hypercalcemia are nonspecific, and the clinician should have a high index of suspicion. Common symptoms include fatigue, anorexia, and constipation. If untreated, a progressive increase in serum calcium level results in deterioration of renal function and mental status. Death ultimately results from renal failure and cardiac arrhythmias.

***Pathologic fractures.*** The destruction of bone by metastatic disease reduces its load-bearing capabilities and results initially in microfractures, which cause pain. Subsequently, fractures occur (most commonly in ribs and vertebrae). It is the fracture of a long bone or the epidural extension of tumor into the spine that causes the most disability. As the development of a long-bone fracture has such detrimental effects on quality of life in patients with advanced cancer, efforts have been made to predict sites of fracture and to preempt the occurrence of a fracture by prophylactic surgery.

Fractures are common through lytic lesions in weight-bearing bones. Damage to both cortical and trabecular bone is structurally important. Several radiological features have been identified that may predict imminent fracture; fracture is likely if lesions are large, are predominantly lytic, and erode the cortex. A scoring system has been proposed by Mirels based on the site, nature, size, and symptoms from a metastatic deposit (26). Using this system, lesions that scored >7 generally require surgical intervention; deposits that scored ≥10 had an estimated risk of fracture of >50%. More sophisticated predictive tools based on computed tomography of sites at risk of fracture are currently under evaluation.

***Compression of the spinal cord or cauda equina.*** Spinal cord compression is a medical emergency, and suspected cases require urgent evaluation and treatment. Pain occurs in most patients, is localized to the area overlying the tumor, and often worsens with activities that increase intradural pressure (e.g., coughing, sneezing, or straining). The pain is usually worse at night, which is the opposite pattern of pain from degenerative disease. There may also be radicular pain radiating down a limb or around the chest or upper abdomen. Local pain usually precedes radicular pain and may predate the appearance of other neurologic signs by weeks or months. Most patients with spinal cord compression will have weakness or paralysis. Late sensory changes include numbness and anesthesia distal to the level of involvement. Urinary retention, incontinence, and impotence are usually late manifestations of cord compression. However, lesions at the level of the conus medullaris can present with early autonomic dysfunction of the bladder, rectum, and genitalia.

In a retrospective analysis of 70 patients with spinal cord compression secondary to breast cancer, the most frequent symptom was motor weakness (96%) followed by pain (94%), sensory disturbance (79%), and sphincter disturbance (61%; ref. 27). Ninety-one percent of patients had at least one symptom for >1 week; 96% of those ambulant before therapy maintained the ability to walk. In those unable to walk, 45% regained ambulation, with radiotherapy and surgery equally effective. Median survival was 4 months. The most important predictor of survival was the ability to walk after treatment. These results suggest that earlier diagnosis and intervention may improve both outcome and survival.

***Spinal instability.*** Back pain is a frequent symptom in patients with advanced cancer and in 10% of cases is due to spinal instability. The pain, which can be severe, is mechanical in origin, and frequently the patient is only comfortable when lying still. Surgical stabilization is often required to relieve the pain, and although such major surgery is associated with considerable morbidity and mortality, excellent results can be obtained with appropriate patient selection.

## Use of Bone Biochemical Markers to Predict Skeletal Morbidity and Clinical Outcome

Metastatic bone disease results from the interactions between cancer cells in the bone marrow microenvironment and normal bone cells. These growth factor and cytokine-mediated interactions lead to stimulation of osteoclastic bone resorption and both uncoupled and unbalanced bone remodeling (28). The effects of cancer on bone cell function can now be assessed accurately by the measurement of specific biochemical markers; for the assessment of bone resorption, these markers are derived from the breakdown of type I collagen, the main protein of bone (29). It is the result of this tumor-induced osteolysis and subsequent loss of the structural integrity of bone that may lead to bone pain, fractures, and other important skeletal complications, rather than stimulation of osteoblastic new bone formation. In other words, the resorptive element of the process largely drives the clinical consequences. However, not all patients with bone metastases experience significant complications, either because of dominant disease at other sites dominating the clinical course or effective control of the skeletal disease by local or systemic treatments.

Recent studies indicate that the risk of skeletal complications in both breast and prostate cancer is strongly related to the rate of bone resorption (30, 31). Such events are uncommon when bone resorption is normal but become increasingly frequent as the bone resorption rate increases. The author's group published a report on the use of the bone resorption marker *n*-telopeptide of type 1 collagen (NTX) that suggested biochemical monitoring was useful in the identification of patients at high risk of skeletal complications. In this relatively short-term study of 121 patients with metastatic

bone disease, monthly measurements of urinary NTX during treatment with a range of bisphosphonates were made (3). All skeletal-related events, plus hospital admissions for control of bone pain, and death during the period of observation were recorded. NTX was strongly correlated with the number of skeletal-related events and/or death ($P < 0.001$). Patients with NTX values above 100 nmol/mmol creatinine were many times more likely to experience a skeletal-related event and/or death than those with NTX values below this level ($P < 0.01$; Table 3).

Subsequently, these data have been confirmed by evaluation of a large data set from patients with bone metastases ($n \geq 3,000$) included in the phase 3 development program of zoledronic acid. In these studies, the relationships between the most recent bone marker measurement and outcome during the next 1 to 3 months were assessed. These analyses showed that elevated NTX levels were highly predictive of skeletal events, progression in bone, and death in both the absence (ref. 31; Table 4) and presence (ref. 32; Table 5) of bisphosphonate treatments. Similar relationships were seen between bone alkaline phosphatase, a bone formation marker (Table 5), and outcome, although NTX was the most predictive. These observations suggested that a more cost-effective use of bisphosphonates might be to delay starting treatment with bisphosphonates until patients have an NTX level above the reference range for a healthy young adult (<50 nmol/mmol creatinine).

Bisphosphonates are potent inhibitors of osteoclast function, and the more potent agents such as zoledronic acid have been shown to reduce skeletal morbidity across a wide range of cancer types that affect bone (33–35). Appropriately, bisphosphonates are increasingly used alongside specific anticancer treatments to prevent skeletal complications, and current international guidelines (American Society of Clinical Oncology) recommend long-term treatment (36). However, bisphosphonates are relatively expensive supportive care drugs, and it is unlikely that health care budgets can support long-term use of bisphosphonates for all cancer patients with metastatic bone disease. It is also somewhat simplistic to assume that all patients require the same dose or schedule of bisphosphonate treatment.

The rate of bone resorption varies both between patients and within patients during periods of disease remission and progression. Patients with normal or only minimally accelerated bone resorption probably do not need the intensity of treatment provided by current schedules of highly potent aminobisphosphonates. Additionally, clinical benefit from bisphosphonates seems to be related to the effective suppression of accelerated bone resorption. Evidence is increasing that the aim of bisphosphonate treatment in advanced cancer (32, 37), as it is in benign bone diseases (38), should be to normalize bone resorption. This suggests that a tailored approach to bisphosphonates therapy may be a more appropriate, safer, and cost-effective approach than the currently licensed and recommended fixed 3- to 4-week schedule of i.v. treatment. This hypothesis is being tested in a large National Cancer Research Institute supported phase 3 clinical trial in the United Kingdom (BISMARK, EudraCT no. 2005-001376-12).

**Table 3.** Rate of bone resorption predicts skeletal complications

| Baseline NTX | Skeletal events and/or death | |
|---|---|---|
| | Total no. patients | Odds ratio (95% confidence interval) |
| 0-50 | 31 | 1 |
| 50-100 | 34 | 1.61 (0.35-7.38) |
| >100-200 | 26 | 14.9 (3.58-62.3) |
| >200 | 30 | 46.7 (10.1-215.4) |

NOTE: Data adapted from ref. 30 and presented as a table.

**Table 4.** Influence of accelerated bone resorption on outcome in the absence of bisphosphonates

| NTX ≥ 100 vs NTX <100 | Relative risk (95% confidence interval) | P |
|---|---|---|
| Hormone refractory prostate cancer ($n$ = 200) | | |
| All SREs | 2.36 (1.30-4.29) | 0.021 |
| Time to first SRE | 2.56 (1.44-4.55) | 0.001 |
| Progressive disease | 2.17 (1.17-4.05) | 0.014 |
| Death | 5.09 (2.90-8.91) | <0.001 |
| Lung cancer and other solid tumors ($n$ = 238) | | |
| All SREs | 3.25 (2.26-4.68) | <0.001 |
| Time to first SRE | 3.05 (1.95-4.72) | <0.001 |
| Progressive disease | 2.02 (1.48-2.74) | <0.001 |
| Death | 4.59 (2.82-7.46) | <0.001 |

NOTE: Data adapted from ref. 31 and presented as a table.
Abbreviation: SRE, skeletal-related event.

## Open Discussion

**Dr. Roodman:** In patients who show no response in bone resorption markers or still have elevated bone resorption markers despite aggressive bisphosphonate therapy, is that simply because their tumor is out of control and not that they are not responding to bisphosphonates?

**Dr. Coleman:** It's probably a surrogate marker for the tempo of the disease, wherever that disease may be. Interestingly, these markers are a better predictor of death than they are of skeletal complications. Most patients don't die directly of their bone disease; they die of their liver disease or wherever their disease is. Nevertheless, these markers are telling us that for whatever reason we're not achieving control of bone resorption and maybe with an alternative therapeutic approach we could improve on that.

**Dr. Roodman:** Looking at the trial of prostate cancer patients, for example, were bone resorption markers going up earlier or sooner than prostate-specific antigen, for example, in these patients? Can this be used as a surrogate for changing therapy rather than adding another bone resorption antagonist?

**Dr. Smith:** We've tried to address this question in a prostate cancer study. One of the ways you might think about is whether these markers are a surrogate for volume of bone disease. We've done multivariate analyses trying to control for all the known

**Table 5.** Influence of continued accelerated bone resorption (urine NTX) on risk of death

| | Relative risk (95% CI) | *P* |
|---|---|---|
| NTX ≥100 vs NTX <50 | | |
| Prostate cancer | 5.72 (4.04-8.11) | <0.001 |
| Breast cancer | 4.84 (3.19-7.32) | <0.001 |
| NSCLC | 3.87 (2.48-6.04) | <0.001 |
| Myeloma | 2.06 (0.25-16.43) | <0.496 |
| Others | 4.54 (2.71-7.58) | <0.001 |
| BAP ≥146 vs BAP <146 IU | | |
| Prostate cancer | 4.22 (2.80-6.35) | <0.001 |
| Breast cancer | 3.73 (2.62-5.29) | <0.001 |
| NSCLC | 1.78 (1.34-2.36) | <0.001 |
| Myeloma | 3.02 (1.54-5.95) | 0.001 |
| Others | 2.23 (1.64-3.03) | <0.001 |

NOTE: Data adapted from ref. 32 and presented as a table.

published prognostic markers. In multivariate analyses, we found that higher levels of BAP but not NTx were independently associated with shorter survival after controlling for known prognostic variables.

**Dr. Coleman:** Are these updated analyses throughout the treatment?

**Dr. Smith:** We restricted the analyses to baseline variables to allow equal consideration of other variables and comparison to other prognostic models.

**Dr. Coleman:** In this data set, we don't have CA15-3, so we're limited to an analysis in prostate cancer, where obviously PSA was measured regularly. There is literature comparing bone markers and tumor markers for response assessment, and neither work very well. Probably bone markers are slightly better in breast cancer than tumor markers.

**Dr. Body:** When both types of markers are high, they are probably better predictors of survival. At early stages of the disease, tumor markers are probably better than bone markers, whether in breast or in prostate cancer.

**Dr. Coleman:** We are focusing on bone-specific treatments. What we've lacked until now is an indicator of what we're achieving in individual patients. All the trials are based on the effects on populations of patients, and yet none of us has a way of saying whether a bisphosphonate is going to benefit an individual patient.

**Dr. Suva:** Can you use the velocity of the increases in the bone markers as a way to track that for a particular patient?

**Dr. Coleman:** Maybe, but we haven't looked at that.

**Dr. Vessella:** In relation to the PSA question, were you asking if it was a good marker of early disease or prognostic? In our data, bone markers are more of an indication of the extent of the disease. When you have very early bone disease, PSA is clearly superior, because you have a background level of the bone markers, showing that in very early disease they seem to be normal. As the disease progresses in the bone, then they begin to increase. There's a correlation with bone burden, but not as an early diagnostic or prognostic marker of bone disease.

**Dr. Coleman:** I don't think there's any way that bone markers would be used as a diagnostic tool for bone metastases, because you can imagine the disruption caused by one small metastasis in the bone compared with the background of normal bone physiology and all the treatments we give would be overwhelmed.

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