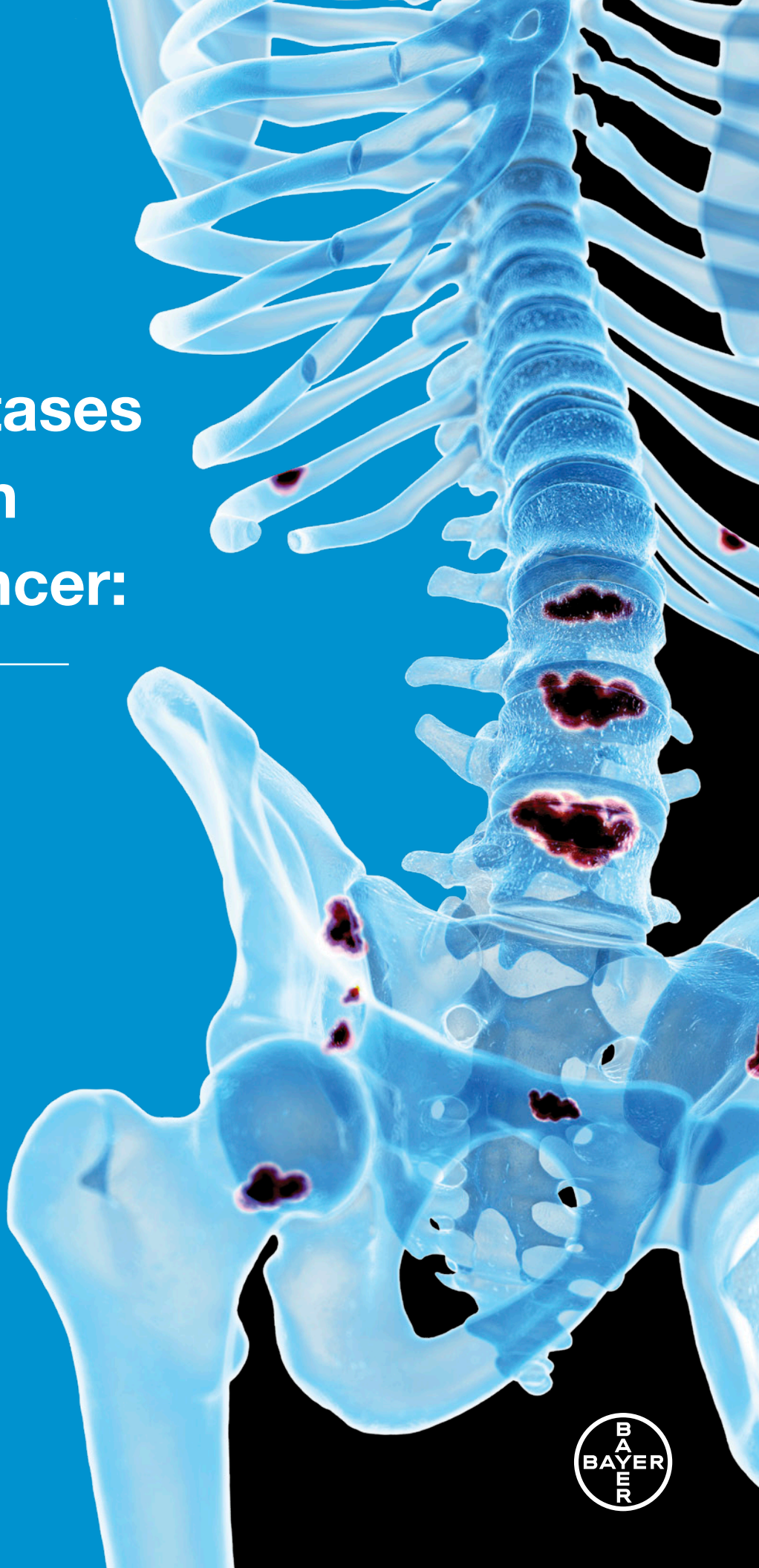
Bone Metastases & Mortality in Prostate Cancer:

Can We Be Doing More?



BAYER

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FOREWORD

Malignant cells are widely disseminated in men with advanced prostate cancer, yet metastases preferentially develop in the bones of the axial skeleton. Approximately 90% of men with advanced prostate cancer develop bone metastases, and the majority who develop these metastases do so many years following removal of the primary tumor, indicating that the site/location of prostate cancer and the disease itself evolves over time.

In advanced prostate cancer, bone metastasis is a killer. Bone metastases are associated with significant mortality and multiple clinical symptoms, including fatigue, which also negatively impacts quality of life. Because advanced prostate cancer is a disease that predominantly resides in the bones, it's appropriate to focus on how clinicians might do more to optimally manage bone metastatic disease. This monograph provides health care professionals with an overview of this significant event in advanced prostate cancer and suggests a strategy to improve patient management.

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EPIDEMIOLOGY & PATHOPHYSIOLOGY: mCRPC

Prostate Cancer Is the Second Most Common Cancer Among US Males

Despite significant recent advances, prostate cancer remains the most common cancer among men in the United States (US).[1,2] Prostate cancer represents 21% of all new cancer cases in men[1] and is responsible for 1 in 5 new cancer diagnoses.[1] In 2015, an estimated 220,800 men in the US were diagnosed with prostate cancer,[2] and approximately 10%-20% of them will develop castration-resistant prostate cancer (CRPC), an advanced form of the disease, within 5 years of follow-up.[3] There are approximately 40,000 men living with metastatic CRPC (mCRPC) in the US.[4]

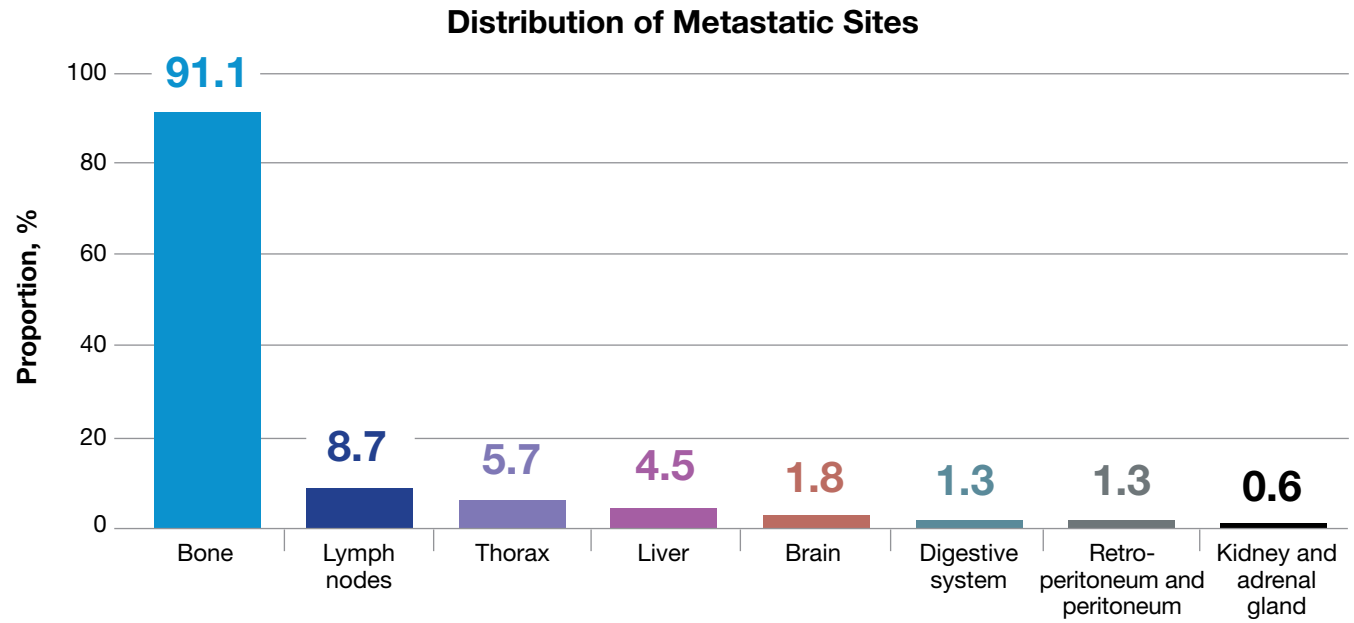
Prostate cancer is the second most common cause of death from cancer in men after lung/bronchus cancer.[1] It is estimated that 26,120 men will die of prostate cancer in 2016.[5] Prostate cancer remains a focus of cancer care management.

Studies have shown that approximately 90% of men with advanced prostate cancer will develop bone metastases.[6,7] This incidence was demonstrated in an autopsy study of 1589 men who had either prostate cancer at autopsy or a history of prostate cancer that was previously treated.[7] In addition, a Surveillance, Epidemiology, and End Results (SEER) database analysis of patients diagnosed with stage IV prostate cancer between 1991 and 2009 also revealed that the majority of patients had bone metastases (91.1%; **Figure 1**).[6] The results showed that while 2.8% of men had lymph node metastases, and 6.1 had visceral metastases, 80.2% had bone metastases, with bone *and* visceral metastases present in another 10.9% of patients[6] (**Figure 1**).

> **Studies have shown that** approximately 90% of men with advanced prostate cancer will develop bone metastases.[6,7]

While it's estimated that 40,000 men diagnosed with prostate cancer will have metastatic disease,[4] the diagnosis of mCRPC is often missed.[8,9] In a clinical trial, Yu et al found a substantial proportion (>30%) of patients with CRPC who were thought to be non-metastatic (M0) were, in fact, metastatic (M1).[8,9]

Figure 1. Distribution of Sites of Metastases in 2607 Men Diagnosed With Stage IV Prostate Cancer Within the SEER–Medicare Database Between 1991 and 2009[6]



The authors noted that there can be uncertainty about the presence of metastatic disease, and that non-metastatic CRPC should be viewed as micrometastatic disease in bone at levels below the detection limits of standard radiological imaging.[8] They also recommend that comprehensive imaging to determine the presence or absence of metastases be undertaken when assessing subjects with prostate cancer for enrollment in future clinical trials, in order to avoid contaminating the study population with subjects who have bone metastases.[8]

Progression to mCRPC upon diagnosis of CRPC can be rapid.[10] Analyses of data from 331 men with CRPC from the placebo group of the Abbott M00-244 trial showed that at 2 years, approximately 50% of men had developed bone metastases and 20% had died.[10] The median survival duration for patients with a diagnosis of CRPC varies from 9 to 30 months.[3] Multivariate analyses showed that a baseline prostate-specific antigen (PSA) of ≥13.1 ng/mL was associated with a shorter time to first bone metastasis (relative risk [RR], 1.98; 95% confidence interval [CI], 1.43-2.74; $P<0.0001$), overall survival (RR, 2.34; 95% CI, 1.71-3.21; $P<0.0001$), and bone metastasis-free survival (RR, 1.98; 95% CI, 1.45-2.70; $P<0.0001$).[10] Greater baseline PSA and PSA velocity, defined as the slope of regression line of natural log PSA by time over the first 12 weeks of follow-up, were associated with shorter time to metastases.[10] These findings underscore the importance of ongoing vigilance for progression to bone metastatic disease.

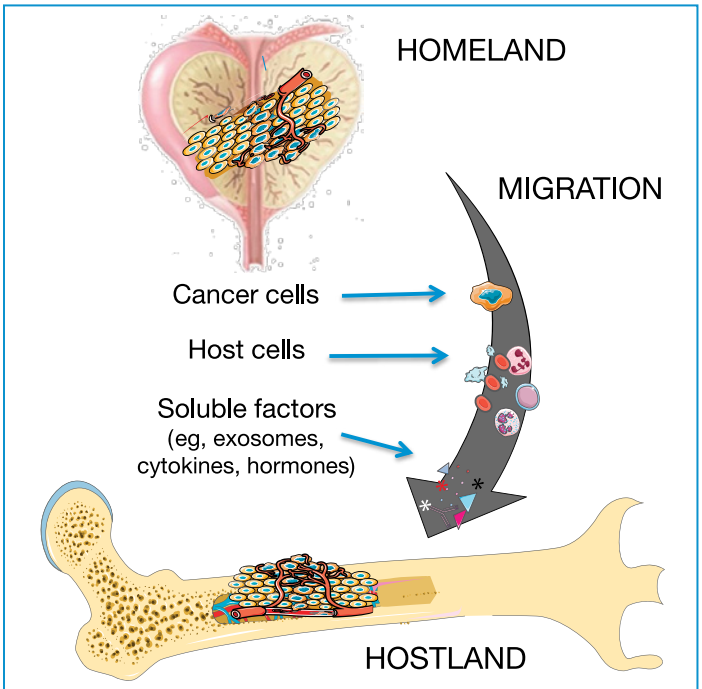
At 2 years, approximately 50% of men with CRPC had developed bone metastases.[10]

Advanced Prostate Cancer Is a Disease That Predominantly Resides in the Bones

In the early stages of advanced prostate cancer, malignant cells shed from the primary tumor migrate locally, invade blood vessels, and may disperse widely in the body.[11-13] Once in the bloodstream, the chances of metastatic cells surviving in many regions of the body outside of the primary tumor (ie, the "Homeland") are low due to the rigorous characteristics of lymphatic and blood circulatory systems and the host defense mechanisms.[11] Prostate cancer cells (the "seeds") in the bloodstream need to settle in an appropriate "soil," and so they preferentially migrate to bone (the "Hostland"; **Figure 2**).[11-13] These malignant cells invade and eventually proliferate in the bones of the axial skeleton, such as the ribs, pelvis, and spine, where red marrow is most abundant,[11,12] although metastases in the long bones and skull are not uncommon.[7,12]

Prostate cancer cells (the "seeds") in the bloodstream need to settle in an appropriate "soil," and so they preferentially migrate to bone.

Figure 2. Prostate Cancer Has an Affinity to Metastasize to Bone[13]



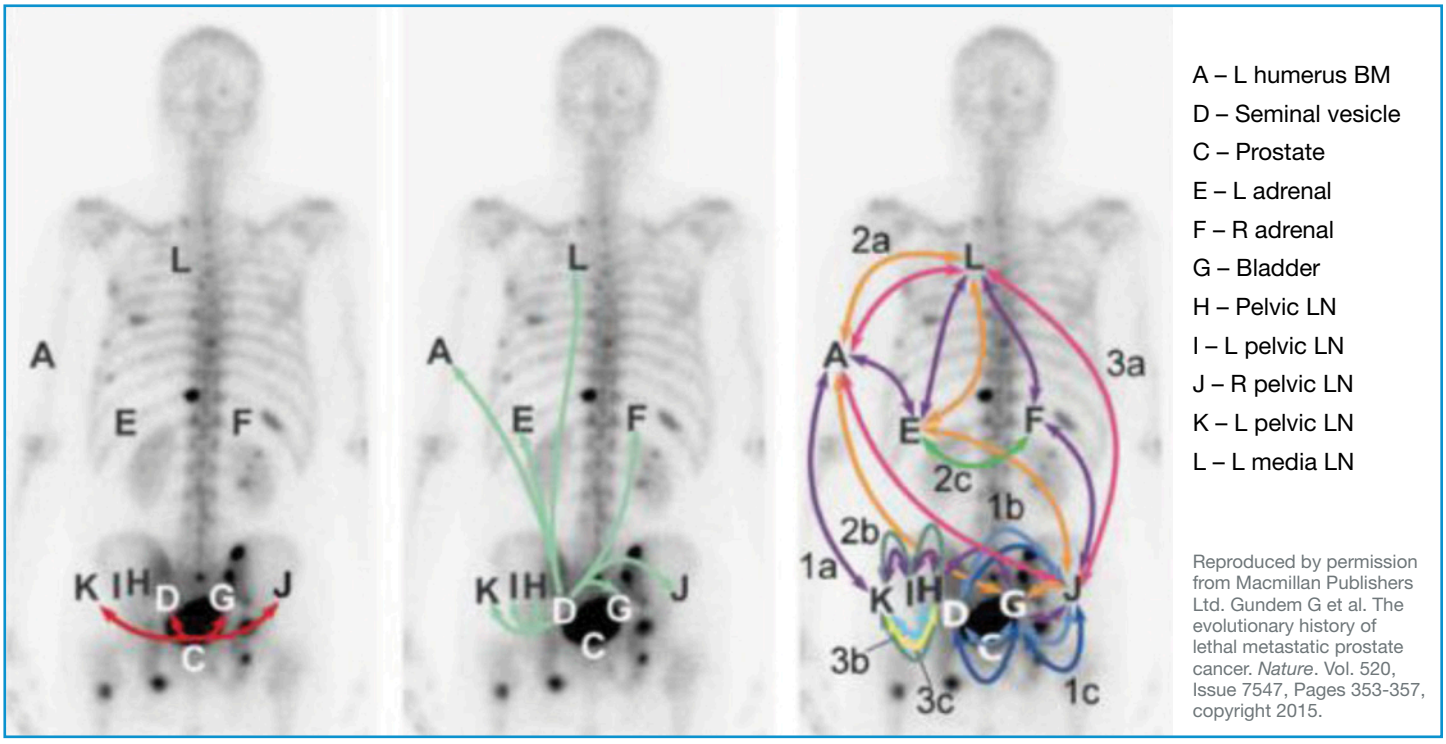
Prostate cancer cells leave the primary tumor (the "homeland") and enter in the bloodstream, where soluble factors aid in their preferential migration to bone (the "hostland").[11,12] Once a prostate cancer cell reaches the skeleton, it still needs to invade the bone and proliferate.[11] The bone matrix is rich in factors that stimulate the growth of tumor cells and promote a vicious cycle of metastases and bone pathology.[11-13] Physical factors in the bone microenvironment, including a supportive vascular system, may also enhance tumor growth.[13]

The physical characteristics of bone tissue – including a supportive vascular system in the axial skeleton, thin sinusoidal walls, a direct venous system from prostate to bone, and slow circulation – can facilitate the attraction and migration of tumor cells to bones.[11] Prostate cancer cells that migrate to the skeleton attach to the endosteal surface and colonize bone.[12] Paget's hypothesis then predicts that the growth of tumor foci tends to be the direct result of a specific organ's microenvironment.[11,13] The bone microenvironment, made up of osteoclasts, osteoblasts, the mineralized bone matrix, and many other types of cells, is highly favorable for tumor invasion and growth.[13] The bone matrix is rich in factors that stimulate the growth of tumor cells and promotes a vicious cycle of metastases and bone pathology (**Figure 2**).[11-13] Bone is an extremely fertile "soil" for prostate cancer "seeds" because a variety of growth factors stored in the matrix are readily released in their active form into the bone microenvironment during the process of physiologic bone remodeling.[11,13] Many cytokines and growth factors are locally released from bone, providing an excess supply of nutrients that can help survival, growth, and spread of the tumor cells.[11]

Bone Metastases May Demonstrate Variable Migratory Pathways

The majority of men with clinically localized prostate cancer who develop bone metastases do so many years following removal of the primary tumor.[14] This indicates a lag between initial therapy and the first indication of future overt metastasis (biochemical recurrence).[14] It is hypothesized that metastatic prostate cancer cells can remain dormant in the bone marrow for several years prior to turning to a proliferative phenotype, a

Figure 3. Bone Metastases May Demonstrate Variable Migratory Pathways[15]



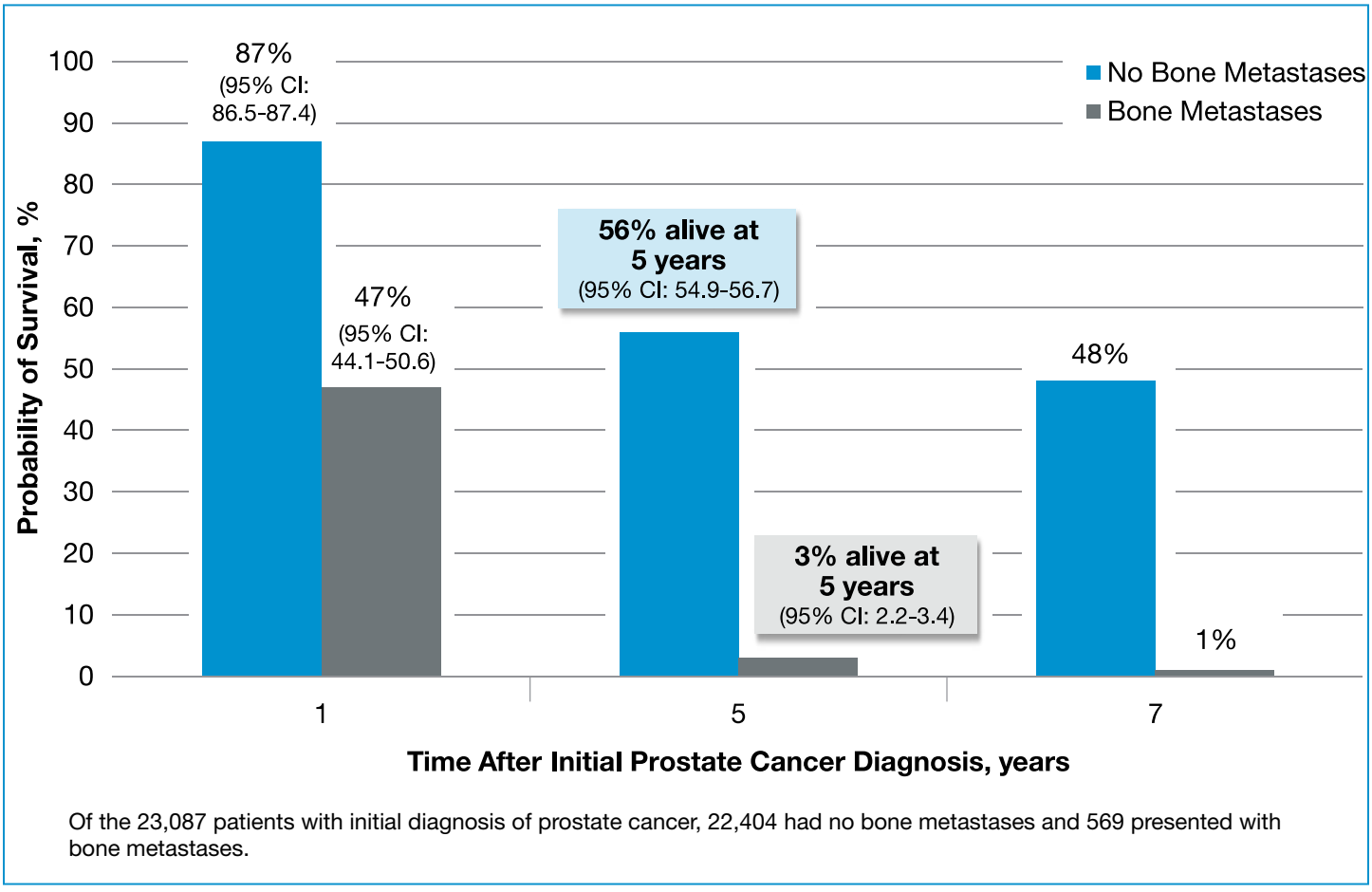
Body maps show the seeding of all tumor sites from one patient in the genomic sequencing study. Seeding events are represented with color-coded arrows and with double-heads when seeding could be in either direction. When the sequence of events may be ordered from the acquisition of mutations, arrows are numbered chronologically. Subclones on branching clonal lineages are labeled with the same number but with different letters, eg, 1a and 1b. Results from these genomic studies support the theory of progression to a proliferative phenotype following dormancy in the bone marrow, as monoclonal and polyclonal metastatic tumor cells are observed to preferentially and frequently migrate between sites distant from the primary tumor.

transformation that drives metastatic progression.[14] The genomic evolution of CRPC, from initial tumorigenesis through the acquisition of metastatic potential to the development of castration resistance, has been revealed by whole genome sequencing.[15] Results from genomic studies support the theory of progression to a proliferative phenotype following dormancy in the bone marrow, as monoclonal and polyclonal metastatic tumor cells are observed to preferentially and frequently migrate between sites distant from the primary tumor (**Figure 3**).[15] The "seed and soil" hypothesis states that metastatic potential is not a property of the primary tumor as a whole, but is acquired as a rare event inside the tumor.[15] Genomic studies also support this hypothesis, as separate waves of metastatic invasion directly from the primary tumor have not been observed.[15]

Bone Metastases Are Associated With Higher Mortality

Bone metastasis indicates a poor prognosis in men with prostate cancer.[16] The 1-year survival rate in a cohort study was 87.0% (95% CI, 86.5-87.4) in men with prostate cancer without bone metastasis, 47.4% (95% CI, 44.1-50.6) in men with bone metastasis but no skeletal-related events (SREs), and 39.9% (95% CI, 35.6-44.2) in men with bone metastasis and SREs.[16] Respectively, corresponding 5-year survival rates in these groups were 55.8% (95% CI, 54.9-56.7), 2.7% (95% CI, 2.2-3.4) and 0.7% (95% CI, 0.6-1.0).[16] **Figure 4** shows the survival probabilities at 1, 5, and 7 years in 2 distinct cohorts of patients with prostate cancer from the cohort study. The men were identified from 1999 through 2007 in the Danish National Patient registry.[16]

Figure 4. Bone Metastases Leads to Poor Survival[16]



Of the 23,087 patients with initial diagnosis of prostate cancer, 22,404 had no bone metastases and 569 presented with bone metastases.

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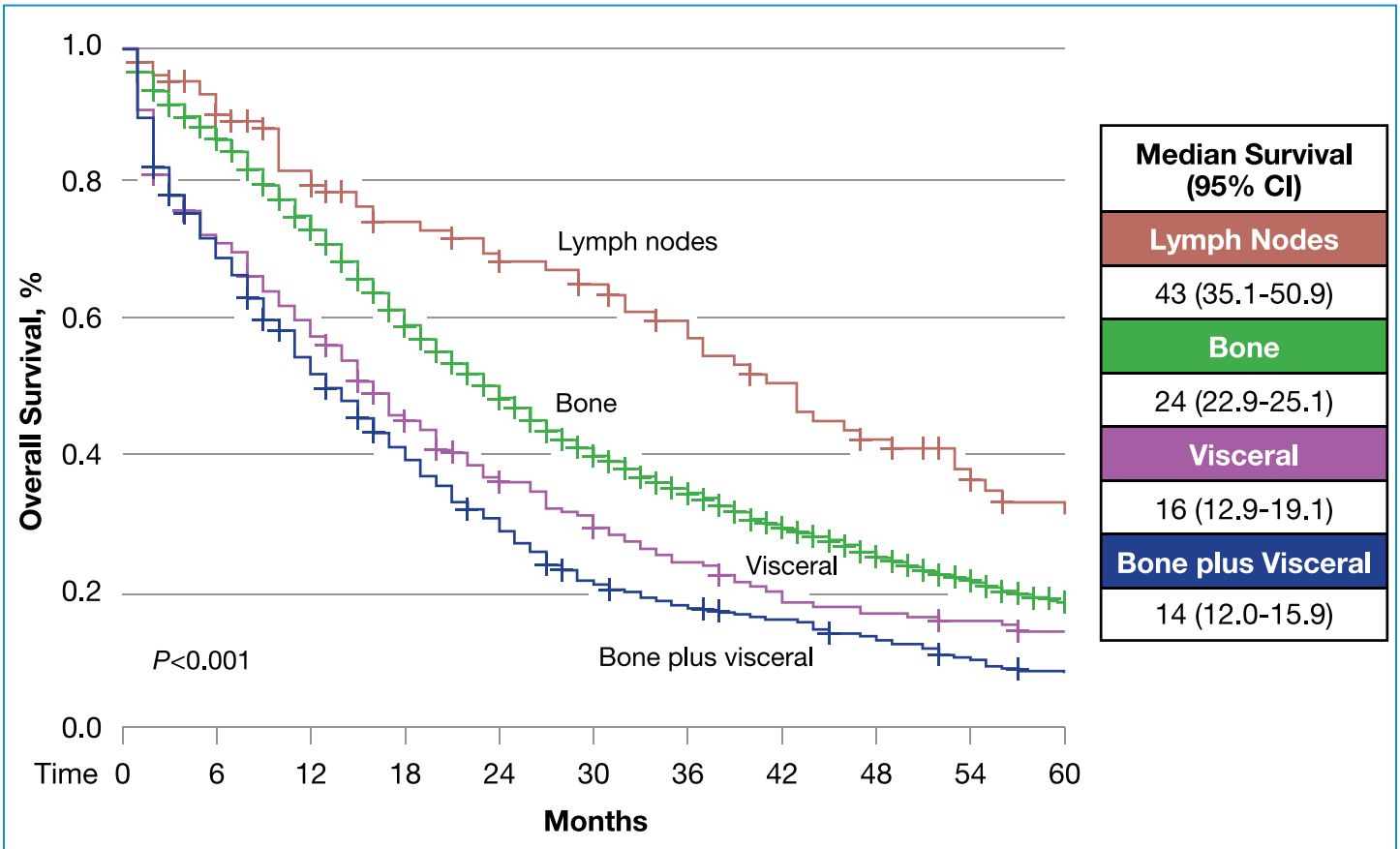
Progression From Bone to Multiple Metastatic Sites Decreases Survival in CRPC

The location of metastases and the number of metastatic sites in patients with prostate cancer may have prognostic implications.[6] The role of the metastatic phenotype on mortality in men with stage IV prostate cancer was examined in 3857 men from the SEER database who presented with metastatic prostate cancer between 1991 and 2009.[6] At diagnosis, 611 patients (15.8%) were identified as having 2 or more metastatic sites. In addition, 108 patients (2.8%) were recorded as having lymph node metastases, 3093 (80.2%) had bone metastases, 234 (6.1%) had visceral metastases, and 422 (10.9%) had bone plus visceral metastases. Progression from bone to multiple metastatic sites is associated with increasing mortality (**Figure 5**).[6]

The site of metastases, after adjusting for confounders, was observed to be an independent prognostic factor.[6] Of note, patients who had bone metastases alone had a 1.5-fold higher probability of dying versus men with lymph node involvement only (P=0.02).[6] Men with bone plus visceral metastases had a 1.3-fold higher probability of dying compared with men who only had bone metastases (P<0.001).[6]

Patients who had bone metastases alone had a 1.5-fold higher probability of dying versus men with lymph node involvement only (P=0.02).[6]

Figure 5. Progression From Bone to Multiple Metastatic Sites Decreases Survival in CRPC[6]



Kaplan-Meier curve depicting time to overall mortality after stratifying patients according to the site of metastases.

OPTIMIZING THE EVALUATION OF BONE METASTASES

Men with advanced prostate cancer are often considerably burdened with symptoms, which may cause significant changes in health-related quality of life (HRQOL).[17] Disease burden is inversely related to HRQOL in men with prostate cancer.[17] Men with poor prognosis metastatic disease and hormone-resistant disease reported significantly worse physical functioning scores, role functioning scores, pain scores, and global health status than men with locoregional disease.[17]

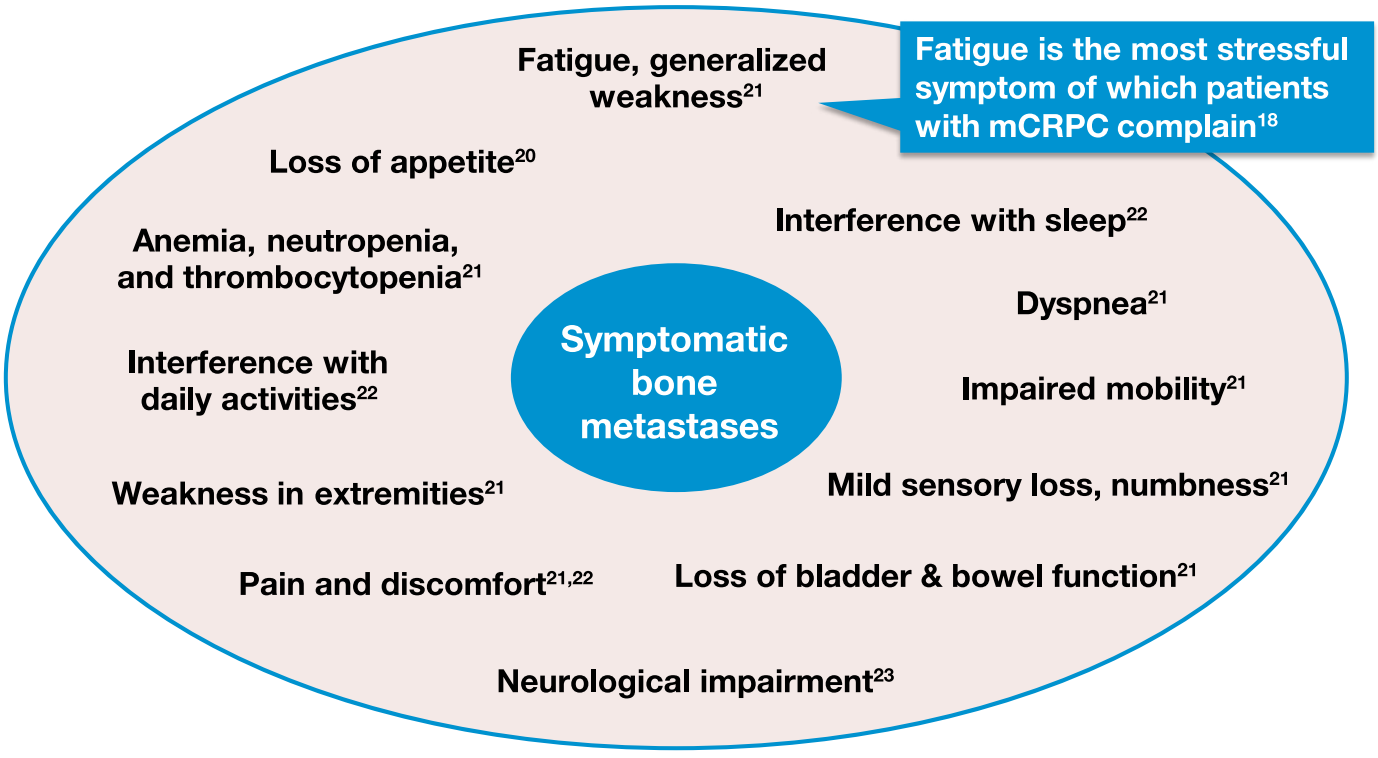
Bone Metastases Have Multiple Symptoms

Most men with mCRPC experience mental and physical morbidity and a decreased HRQOL.[18] Multiple symptoms are associated with bone metastases (**Figure 6**), yet a recent Prostate Cancer Symptoms Survey revealed that nearly 7 of 10 patients (68%) ignore their symptoms.[19] Therefore, a complete review/discussion of patient history is critical to reveal symptoms associated with bone metastatic disease in advanced prostate cancer. In a US survey of men with advanced prostate cancer, the most common symptoms reported by men with bone metastases include[19]:

- Fatigue: 85%
- All over body pain or aches: 55%
- Numbness or weakness: 55%
- Difficulty sleeping as a result of pain: 42%
- Difficulty doing normal activities: 40%
- Anxiety or distress as a result of pain: 40%
- Vomiting: 25%[20]
- Loss of appetite: 20%[20]

68% of patients
ignore their symptoms.[19]

Figure 6. Multiple Symptoms Are Associated With Bone Metastases[18,20-23]



Fatigue is the most stressful symptom of which patients complain.[18] They report that fatigue influences their daily functioning more so than any other symptom.[18] Fatigue can be attributed to mCRPC, the adverse effects of mCRPC treatments, decreased activity, poor nutrition, depression, and comorbid conditions.[18] Pain and discomfort can vary in nature and severity and is often accompanied by fatigue.[21]

> **Fatigue is the most** stressful symptom of which patients complain.[18]

Bone metastases in the spine, pelvis, and femur may affect mobility.[21,24] Patients with bone metastases in these locations may have problems sitting, walking, or being able to lie in a comfortable position.[21] Bone metastases located in the cervical spine, humerus, or shoulder can impact range of movement, and may compromise activities of daily living.[21] A decrease in mobility also raises the risk of respiratory infections and thromboembolism.[21]

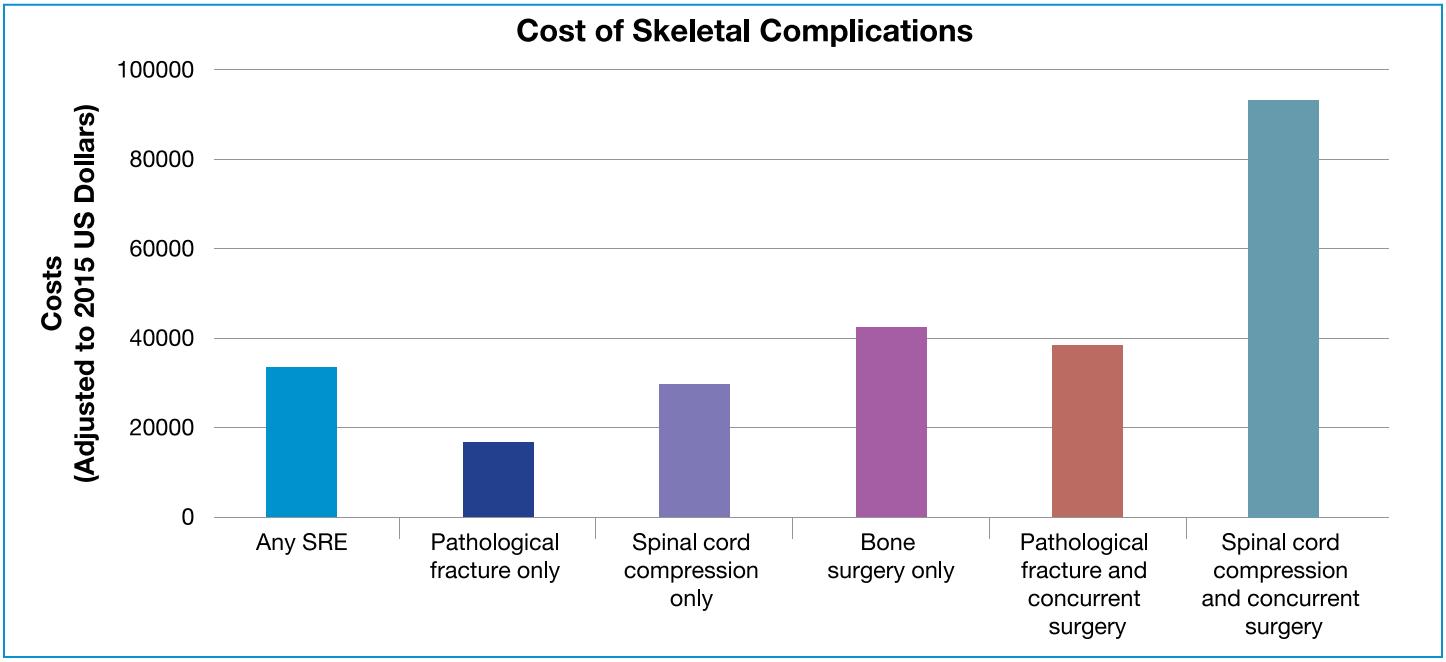
Weakness or numbness in the legs, and problems with the bladder and bowel could be caused by the pressure of bone metastases on the spinal cord.[21] Spinal cord compression represents an oncological emergency, and early diagnosis and treatment is necessary for successful rehabilitation.[21] If left untreated, neurological damage can occur, ranging from mild sensory impairment to complete paraplegia, with loss of bowel and bladder function.[21,23] Neurological recovery is unlikely if spinal cord compression is not relieved within 24-48 hours.[21]

Anemia, neutropenia, and thrombocytopenia may also be caused by bone marrow involvement, which can increase fatigue, general weakness, and dyspnea. Abnormal bleeding or bruising can occur if platelets are low.[21] Men with advanced prostate cancer may also have hypercalcemia (a serum calcium of more than 2.6 mmol/L), which develops due to the increased release of calcium from bone and kidney dysregulation.[21] Common symptoms of hypercalcemia include nausea, reduced appetite, increased thirst, and fatigue and confusion. If left untreated, hypercalcemia can result in arrhythmias, coma, and death.[21]

Bone Metastatic Disease: A Significant Economic Burden

A model that draws upon the SEER database estimates the lifetime costs of prostate cancer for men ≥65 years old who were diagnosed from 1991 to 2002. The model showed a lifetime medical care cost of $140,501 (95% CI, $140,252-$140,780) per person (standardized to 2015 US dollars).[25] Men who were stage 0 or whose cancer stage at diagnosis could not be identified were excluded from

Figure 7. Bone Metastatic Disease: A Significant Economic Burden[26]



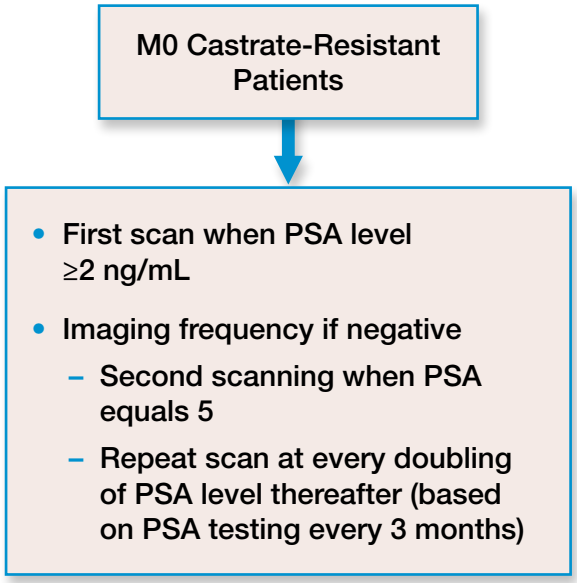
this model.[25] Skeletal complications caused by prostate cancer metastases to bone are an important public health concern due to their association with reduced survival, notable morbidity, diminished HRQOL, and increased health care costs (**Figure 7**).[26] In a matched case-control study conducted to investigate health care utilization costs among elderly stage IV metastatic (M1) prostate cancer patients, the highest yearly health care cost was noted for men with spinal cord compression with concurrent surgery, followed by surgery to bone only, and pathological fracture with concurrent surgery.[26] Proactive monitoring and intervention of bone metastatic disease can reduce/prevent skeletal complications.[26]

IS EARLIER DETECTION OF BONE METASTATIC DISEASE OF VALUE?

RADAR: Identify Metastatic Disease Early in M0 Castration-Resistant Patients

Current methods for the initial detection of bone metastases may be suboptimal,[9] and strategies for the early identification of metastases in patients with prostate cancer have been recommended by the Radiographic Assessments for Detection of Advanced Recurrence Group (RADAR).[3] This group has made recommendations on imaging criteria and imaging frequency for different patient groups with prostate cancer; those recommendations could lead to the early identification of metastatic disease in M0 patients (**Figure 8**).[3]

Figure 8. Key Recommendations From the RADAR Group for the Early Identification of Metastatic Disease in M0 Patients[3]



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When considering cost effectiveness, the RADAR Group recommended conventional bone scintigraphy using technetium 99 (^{99m}Tc) and abdomen/pelvis/chest computed tomography (CT) as the imaging modalities for initial testing.[3] Other novel imaging modalities are available (**Table 1**), and the RADAR group suggested that plain radiography, magnetic resonance imaging (MRI), and ^{18}F-Sodium Fluoride positron emission tomography/CT (NaF PET/CT) should be conducted at the physician's discretion when necessary, as they might be needed to clarify equivocal lesions.[3] PET/CT scans using tracers, such as ^{18}F-NaF, show sensitivity and specificity values superior to bone scintigraphy (**Table 1**) and are frequently incorporated into guidelines.[3]

Table 1. Available Imaging Technologies[27,28]

Imaging Test	Sensitivity (%)	Specificity (%)
^{99m}Tc[27]	78	48
^{18}F–NaF PET/CT[27]	100	97
MRI[27]	95	90
CT[27]	74	56
PSMA[28]	66	96

PSMA, prostate-specific membrane antigen.

The Use of ALP and PSA Is an Effective Tool for Predicting Risk of Bone Metastatic Disease

Bone alkaline phosphatase (ALP) in combination with PSA can be an effective marker for predicting the risk of developing bone metastatic disease.[29] Multivariate analyses from a study to identify predictors of bone metastatic disease in 203 individuals with asymptomatic, treatment-naive prostate cancer identified ALP and PSA as being independent predictors of bone metastases (**Table 2**).[29] The combination of elevated ALP and PSA (in which patients with either elevated PSA [>20 ng/mL] OR elevated ALP were considered as positive) had the best screening value for the detection of bone metastases, with a sensitivity of 98.2% and a specificity of 48.6%.[29] The risk factors identified in this study and the recommendations provided by the RADAR group may be used to detect the onset of bone metastases in asymptomatic patients.[3,29]

Monitor Key Bone-Related Parameters as Prognostic Factors for Overall Survival

Several bone-related parameters including those listed in **Table 3** have been demonstrated to be individual prognostic variables for overall survival in patients with bone metastases from CRPC (**Table 3**).[30] In an analysis of the prognostic value of multiple parameters in 1901 patients with mCRPC enrolled in an international, multicenter, randomized, double-blind phase 3 trial, the following bone-specific parameters were significantly associated with longer survival: ALP ≤143 U/L (P<0.0001); bone-specific alkaline phosphatase (BSAP) <146 U/L (P<0.0001); corrected urinary N-telopeptide (uNTX) ≤50 nmol/mmol (P<0.0008); mild or no pain (Brief Pain Inventory—Short Form [BPI-SF] score ≤4) (P<0.0001); no previous SRE (P=0.0002); longer time from initial diagnosis of

Table 2. Relation Between Different PSA Levels, ALP Levels, and Bone Metastases[29]

PSA		ALP	*P* Value
<20	Bone Metastasis (n=6)	345.3 ± 109.9	0.01
	No Bone Metastasis (n=76)	169.4 ± 61.3	
20-50	Bone Metastasis (n=14)	322.0 ± 146.2	0.01
	No Bone Metastasis (n=46)	181.3 ± 75.1	

Table 3. Bone-Specific Parameters Associated With Significantly Longer Survival[30]

Parameter	Hazard Ratio (95% CI)	*P* Value
ALP ≤143 U/L	0.664 (0.559, 0.789)	P<0.0001
BSAP <146 U/L	0.683 (0.568, 0.822)	P<0.0001
Corrected uNTX ≤50 nmol/mmol	0.755 (0.640, 0.889)	P<0.0008
No previous SRE	0.748 (0.643, 0.871)	P=0.0002
Longer time from initial diagnosis of CRPC to first bone metastasis	0.997 (0.995, 0.998)	P<0.0001
Mild or no pain (BPI-SF score ≤4)	0.648 (0.563, 0.745)	P<0.0001

CRPC to first bone metastasis (P<0.0001); and longer time from first bone metastasis to randomization (P<0.0001; **Table 3**).[30]

CHANGE YOUR CLINICAL APPROACH AS PROSTATE CANCER PROGRESSES

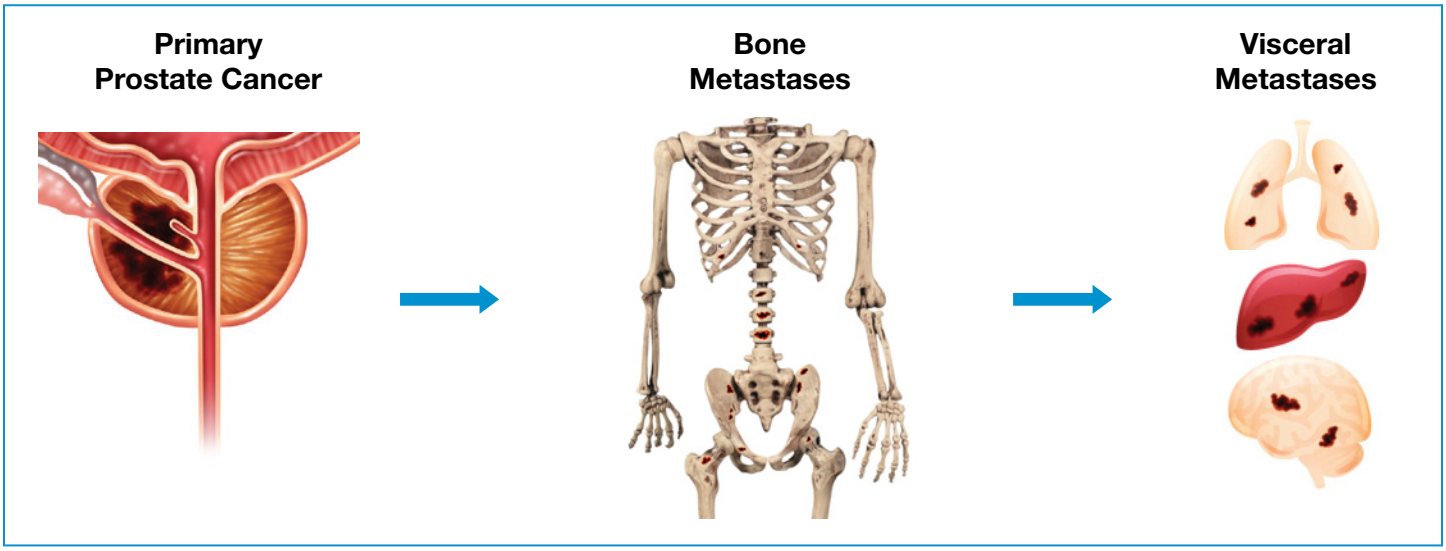
As discussed in this monograph, one of the most important factors influencing the clinical approach to prostate cancer is the presence or absence of metastases.[3] The site/location of prostate cancer evolves/moves over time, which has important implications.[3] When cancer spreads to the bone, reconsider your approach to focus on bone metastases (**Figure 9**). Early assessment of the presence of bone metastasis is important for optimizing patient disease management.

> **When cancer spreads** to the bone, reconsider your approach to focus on bone metastases.

SUMMARY

The site/location of prostate cancer evolves/moves over time, which has important management implications.[3,15] Advanced prostate cancer is a disease that predominantly resides in the bones.[11-13] Approximately 90% of men with advanced prostate cancer will develop bone metastases,[6,7] and the presence of bone metastases indicates a poor prognosis and a higher mortality.[16] Multiple symptoms are associated with bone metastases,[18,20-23] and these symptoms negatively impact quality of life.[17] Fatigue is the symptom men with mCRPC complain about most often, and they report that fatigue influences their daily functioning more so than any other symptom.[18] Early detection of bone metastases can inform clinical decision making and is dependent on laboratory, clinical, and patient symptom assessment. Strategies for the early identification of metastases in patients with prostate cancer have been recommended by the RADAR Group,[3] and ALP plus PSA can be an effective tool for predicting risk of bone metastatic disease.[29] Because mortality increases as the disease migrates from localized to multiple metastatic sites,[6] it is important for clinicians to adjust their clinical approach as prostate cancer progresses.[3]

Figure 9. Change Your Clinical Approach as Disease Progresses[14,15,31]

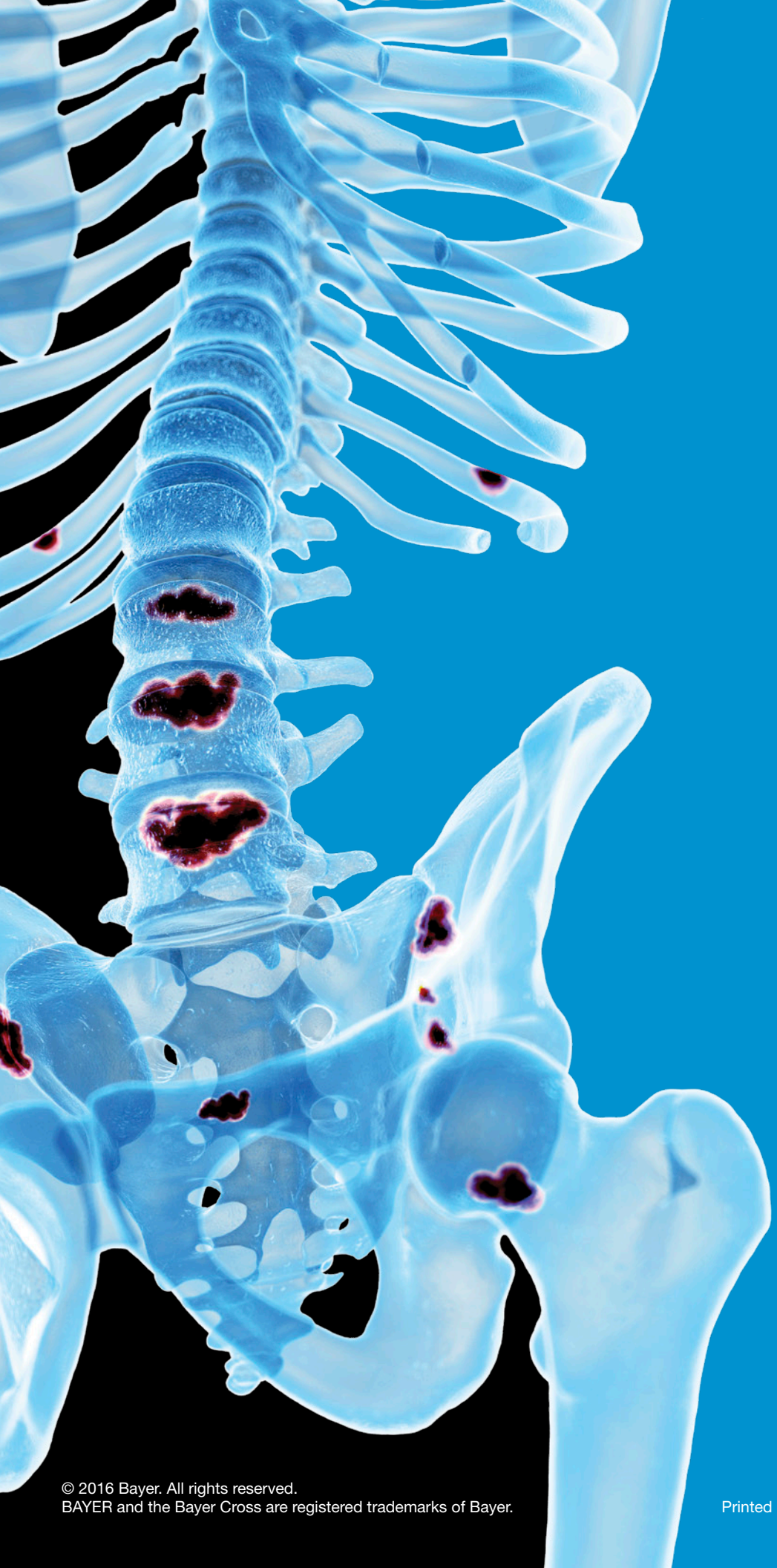


The site/location of prostate cancer evolves/moves over time.[14,15] When cancer spreads to the bone, focus on bone metastatic disease.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30.
2. National Institutes of Health. National Cancer Institute. SEER Stat Fact Sheets: Prostate Cancer. http://seer.cancer.gov/statfacts/html/prost.html. Accessed April 1, 2016.
3. Crawford ED, Stone NN, Yu EY, et al; Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group. Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology*. 2014;83(3):664-669.
4. Scher HI, Solo K, Valant J, et al. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. *PLoS One*. 2015;10(10):e0139440.
5. American Cancer Society. Key statistics for prostate cancer. http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics. Accessed April 1, 2016.
6. Gandaglia G, Karakiewicz PI, Briganti A, et al. Impact of the site of metastases on survival in patients with metastatic prostate cancer. *Eur Urol*. 2015;68(2):325-334.
7. Bubendorf L, Schöpfer A, Wagner U, et al. Metastatic patterns of prostate cancer: an autopsy study of 1589 patients. *Hum Pathol*. 2000;31(5):578-583.
8. Yu EY, Miller K, Nelson J, et al. Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. *J Urol*. 2012;188(1):103-109.
9. Sartor O, Eisenberger M, Kattan MW, et al. Unmet needs in the prediction and detection of metastases in prostate cancer. *Oncologist*. 2013;18(5):549-557.
10. Smith MR, Cook R, Lee KA, et al. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. *Cancer*. 2011;117(10):2077-2085.
11. Bagi CM. Skeletal implications of prostate cancer. *J Musculoskelet Neuronal Interact*. 2003;3(2):112-117.
12. Kingsley LA, Fournier PG, Chirgwin JM, et al. Molecular biology of bone metastasis. *Mol Cancer Ther*. 2007;6(10):2609-2617.
13. Yin JJ, Pollock CB, Kelly K. Mechanisms of cancer metastasis to the bone. *Cell Res*. 2005;15(1):57-62.
14. van der Toom EE, Verdone JE, Pienta KJ. Disseminated tumor cells and dormancy in prostate cancer metastasis. *Curr Opin Biotechnol*. 2016;40:9-15.
15. Gundem G, Van Loo P, Kremeyer B, et al. The evolutionary history of lethal metastatic prostate cancer. *Nature*. 2015;520(7547):353-357.
16. Nørgaard M, Jensen AØ, Jacobsen JB, et al. Skeletal related events, bone metastasis and survival of prostate cancer: a population based cohort study in Denmark (1999 to 2007). *J Urol*. 2010;184(1):162-167.

17. Resnick MJ, Penson DF. Quality of life with advanced metastatic prostate cancer. *Urol Clin North Am*. 2012;39(4):505-515.
18. Colloca G, Venturino A, Governato I, et al. Incidence and correlates of fatigue in metastatic castration-resistant prostate cancer: a systematic review. *Clin Genitourin Cancer*. 2016;14(1):5-11.
19. Bayer. MenWhoSpeakUp. Prostate Cancer Symptoms Survey: US Results, 2015. http://www.menwhospeakup.com/index.php. Accessed April 1, 2016.
20. Hamilton W, Barrett J, Stapley S, et al. Clinical features of metastatic cancer in primary care: a case-control study using medical records. *Br J Gen Pract*. 2015;65(637):e516-522.
21. Farrell C. Bone metastases: assessment, management and treatment options. *Br J Nurs*. 2013;22(10):S4-S11.
22. Autio KA, Bennett AV, Jia X, et al. Prevalence of pain and analgesic use in men with metastatic prostate cancer using a patient-reported outcome measure. *J Oncol Pract*. 2013;9(5):223-229.
23. Selvaggi G, Scagliotti GV. Management of bone metastases in cancer: a review. *Crit Rev Oncol Hematol*. 2005;56(3):365-378.
24. Penson DF, Litwin MS. The physical burden of prostate cancer. *Urol Clin North Am*. 2003;30(2):305-313.
25. Stokes ME, Ishak J, Proskorovsky I, et al. Lifetime economic burden of prostate cancer. *BMC Health Serv Res*. 2011;11:349.
26. Jayasekera J, Onukwugha E, Bikov K, et al. The economic burden of skeletal-related events among elderly men with metastatic prostate cancer. *Pharmacoeconomics*. 2014;32(2):173-191.
27. O'Sullivan GJ, Carty FL, Cronin CG. Imaging of bone metastasis: an update. *World J Radiol*. 2015;7(8):202-211.
28. Mhawech-Fauceglia P, Zhang S, Terracciano L, et al. Prostate-specific membrane antigen (PSMA) protein expression in normal and neoplastic tissues and its sensitivity and specificity in prostate adenocarcinoma: an immunohistochemical study using multiple tumour tissue microarray technique. *Histopathology*. 2007;50(4):472-483.
29. Moslehi M, Cheki M, Salehi-Marzijarani M, et al. Predictors of bone metastasis in pre-treatment staging of asymptomatic treatment-naive patients with prostate cancer. *Rev Esp Med Nucl Imagen Mol*. 2013;32(5):286-289.
30. Fizazi K, Massard C, Smith M, et al. Bone-related parameters are the main prognostic factors for overall survival in men with bone metastases from castration-resistant prostate cancer. *Eur Urol*. 2015;68(1):42-50.
31. Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. Published online March 7, 2016. *J Clin Oncol*. doi:10.1200/JCO.2015.65.7270.



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