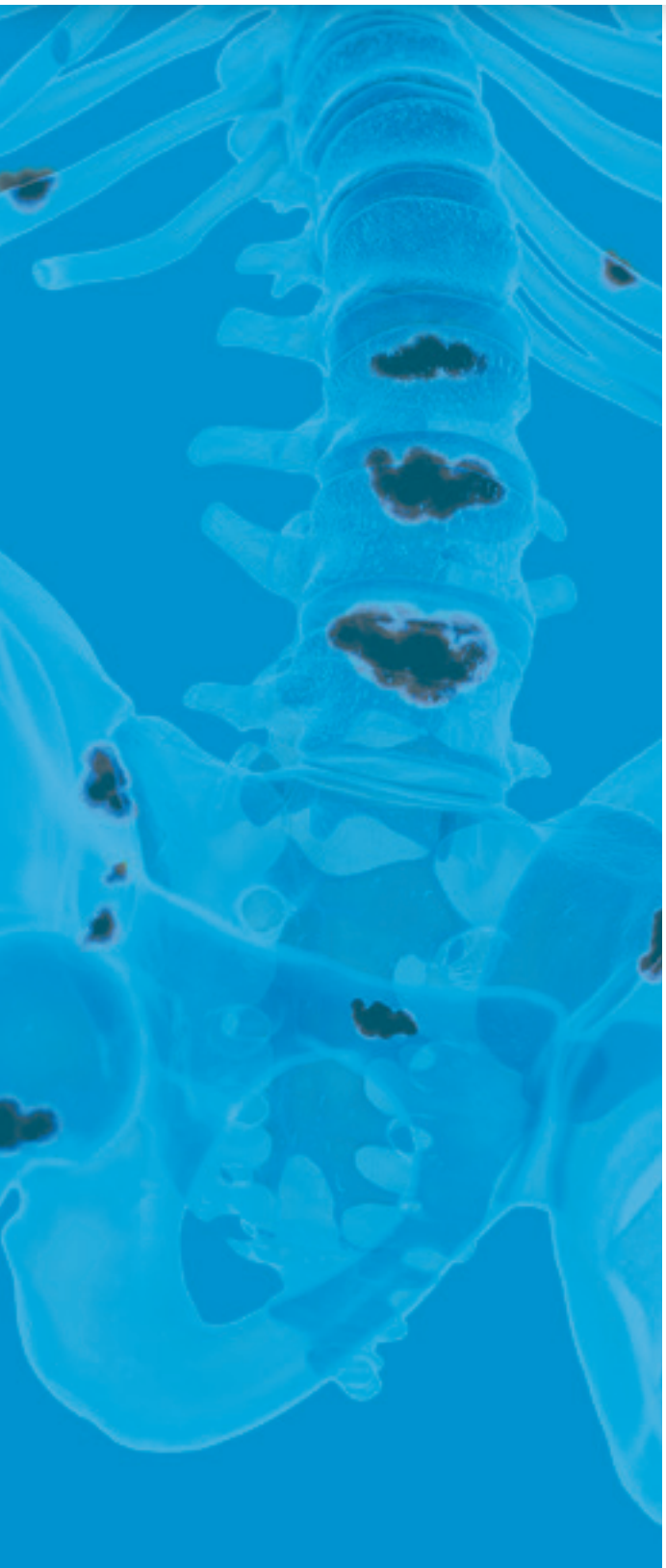
THE IMPACT OF BONE METASTASES IN DRIVING MORTALITY

in Metastatic Castration-Resistant Prostate Cancer

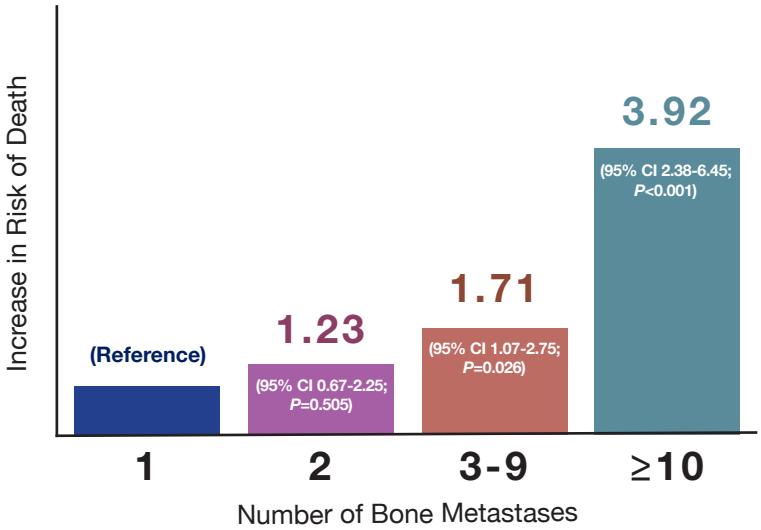


AS THE NUMBER OF BONE METASTASES INCREASES, SURVIVAL DECREASES[1]

Bone metastases are both highly prevalent and highly prognostic in metastatic castration-resistant prostate cancer (mCRPC).[1,2] More than 90% of men with mCRPC will develop bone metastases,[2] and survival in those patients decreases as the number of bone metastases increases.[1]

The inverse relationship between number of bone metastases and survival was documented in a retrospective study of 205 men with mCRPC.[1] Univariate analysis found that men with 10 or more bone metastases had an almost 4-fold increase in risk of death compared with men with one bone metastasis (hazard ratio [HR] for death: 3.92; 95% confidence interval [CI] 2.38-6.45; *P*<0.001).

In mCRPC, More Bone Metastases Mean a Greater Risk of Death[1]



Bone metastases significantly impact mortality in mCRPC.[1]

In Advanced Prostate Cancer,
BONE METASTASES SPAWN MORE METASTASES[3]

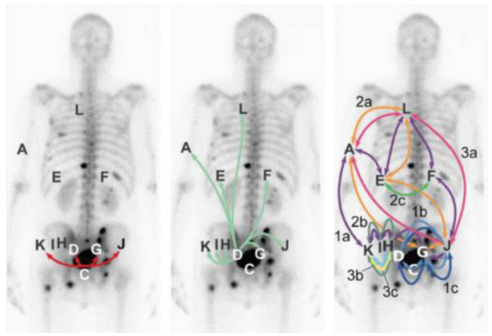
Metastases may spread between distant sites, rather than in separate waves from the primary tumor, in advanced prostate cancer.[3]

That insight into the dissemination of metastases comes from a study in which researchers performed whole genome sequencing on 51 tumors from 10 men with metastatic prostate cancer.[3] The authors observed, "A picture emerges of a diaspora [or migration] of tumor cells, sharing a common heritage, spreading from one site to another, while retaining the genetic imprint of their ancestors."[3]

Bone has long been recognized as a preferential site for the development of metastases in prostate cancer.[4] These findings show that it is also an important "point of departure" to visceral tissues.[3]

The spread of metastases from bone to visceral tissue is significant because a study involving 3857 patients with metastatic prostate cancer found that those with bone plus visceral metastases had shorter median overall survival than those with lymph node–only, bone-only, or visceral-only metastases.[2]

Metastasis-to-Metastasis Seeding in Advanced Prostate Cancer[3]



A - L humerus BM
D - Sem. vesicle
C - Prostate
E - L adrenal
F - R adrenal
G - Bladder
H - Pelvic LN
I - L pelvic LN
J - R pelvic LN
K - L pelvic LN
L - L media. LN

In this body map of a man with metastatic prostate cancer in the genomic sequencing study, arrows show how metastases seed other metastases.[3]

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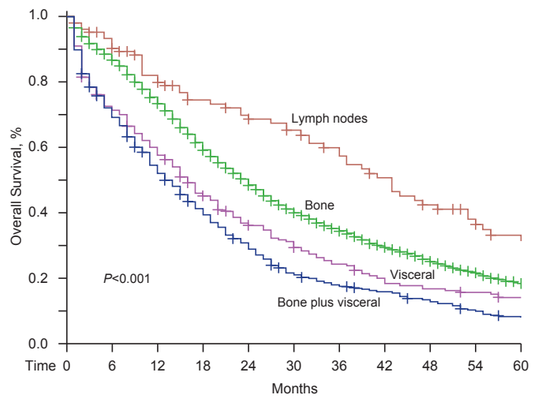
Survival Declines With Progression From Bone-Only to Bone-Plus-Visceral Metastases[2]

Median Survival (95% CI)			
Lymph Nodes	Bone	Visceral	Bone Plus Visceral
43 (35.1-50.9)	24 (22.9-25.1)	16 (12.9-19.1)	14 (12.0-15.9)



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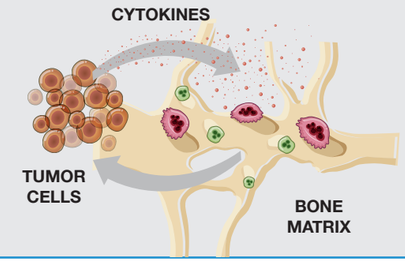
Unaddressed, bone metastases may migrate to multiple sites, negatively impacting survival.[3]

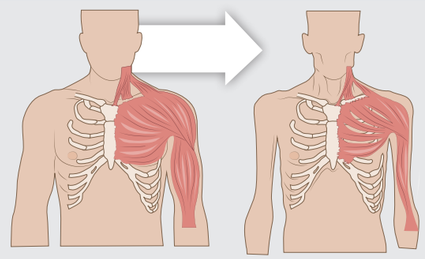
In Advanced Prostate Cancer,
BONE METASTASES DRIVE MORTALITY[5]

Examining How Bone Metastases Drive Mortality in mCRPC[5]

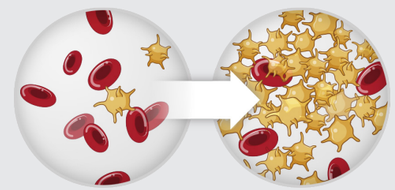
1 "Cross-talk" between malignant cells and the bone microenvironment leads to release of cytokines[6]



2 Proinflammatory cytokines play a central role in the pathogenesis of cachexia[7]



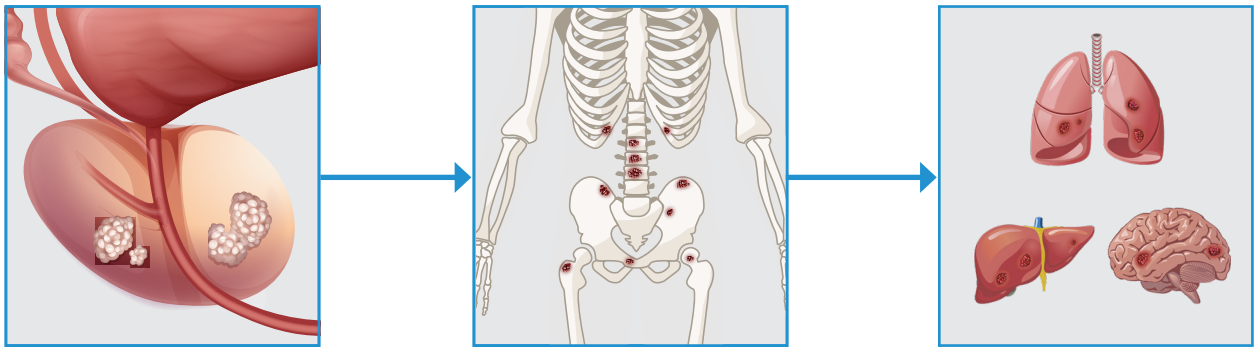
3 Cachexia increases the risk of death through multiple pathophysiologic processes[8-10]



Bone metastases drive mortality in mCRPC through processes set in motion by "cross-talk" between malignant cells and the bone microenvironment.[5-10]

When Prostate Cancer Spreads to the Bone, **RECONSIDER YOUR TREATMENT APPROACH TO FOCUS ON BONE METASTASES**

Treat Primary Prostate Cancer → **Treat Bone Metastases** → **Treat Visceral Metastases**



- As the number of bone metastases increases, survival declines[1]
- In prostate cancer, metastases may spread between distant sites—not as separate waves from the primary tumor—with bone serving as a preferential site for development of metastases and as an important "point of departure" to visceral tissues[3,4]
- Survival decreases with progression from bone-only to bone-plus-visceral metastases[2]
- Bone metastases drive mortality in mCRPC through processes set in motion by "cross-talk" between malignant cells and the bone microenvironment[5-10]

When cancer spreads to the bone—as it does in 90% of men with mCRPC[2]—reconsider your treatment approach to focus on bone metastases.

References

1. Moreira DM et al. *Clin Genitourin Cancer*. 2017;15(1):60-66.e2. **2.** Gandaglia G et al. *Eur Urol*. 2015;68(2):325-334. **3.** Gundem G et al. *Nature*. 2015;520(7547):353-357. **4.** Kingsley LA et al. *Mol Cancer Ther*. 2007;6(10):2609-2617. **5.** Jin J-K et al. *Int J Cancer.* 2011;128(11):2545-2561. **6.** D'Amico L, Roato I. *J Immunol Res*. 2015;2015:143526. **7.** Morley JE et al. *Am J Clin Nutr*. 2006;83(4):735-743. **8.** Kalantar-Zadeh K et al. *J Cachexia Sarcopenia Muscle*. 2013;4(2):89-94. **9.** Donohoe CL et al. *Gastro Res Prac*. 2011;2011:601434. **10.** Biswas AK, Acharyya S. *Annu Rev Cancer Biol*. 2020;4:391-411.

PP-PF-ONC-US-1739-1 04/21