Timing and Optimization of Radium 223 in CRPC

Banner MD Anderson Cancer Center

Making Cancer History®

Disclosures

- Bayer
- Janssen

Objectives

- Significance of bone metastases
- Symptoms associated with bone mets
- Early identification of bone metastases
- Therapeutic layering
- Assessment for progression

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

- Malignant cells are widely disseminated in advanced prostate cancer[1]
- Metastases preferentially develop in bones where red marrow is most abundant[2]
  - Spine
  - Pelvis
  - Ribs
- Metastases may also occur in the skull and long bones[2,3]

Source: Gabriel Sotomayor[4]

1. van der Toom EE. *Curr Opin Biotechnol*. 2016;40:9-15. 2. Bagi CM. *J Musculoskelet Neuronal Interact*. 2003;3(2):112-117. 3. Bubendorf L et al. *Hum Pathol*. 2000;31(5):578-583. 4. Sotomayor GL. *Medwave.* 2003;3(7):e3294. doi: 10.5867/medwave.2003.07.3294. Accessed June 28, 2016.

Prostate Cancer Has an Affinity to Metastasize to Bone[1]

- The bone matrix is rich in factors that stimulate the growth of tumor cells and promotes a vicious cycle of metastases and bone pathology[1]

- Physical factors in the bone microenvironment may also enhance tumor growth

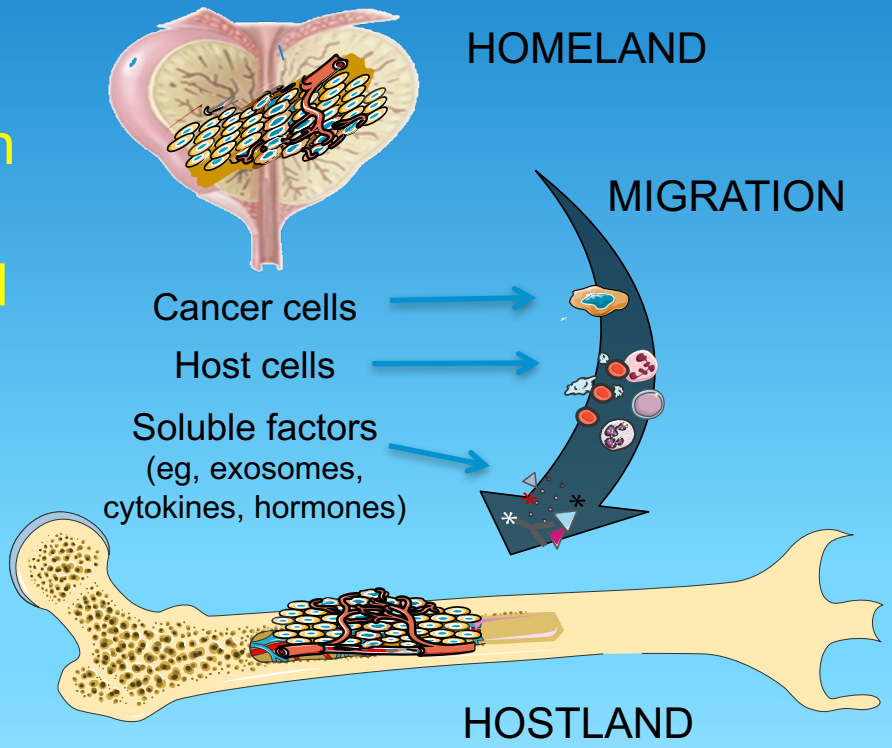
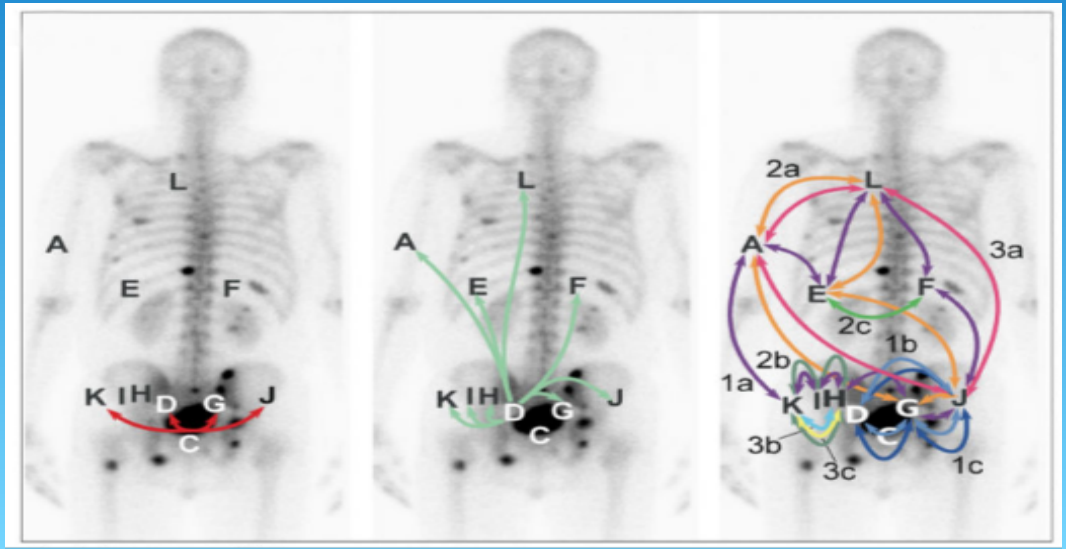


Image courtesy of Kenneth Pienta, MD.

1. Yin JJ et al. *Cell Res.* 2005;15(1):57-62.

Bone Metastases May Demonstrate Variable Migratory Pathways

- Metastases usually spread between distant sites rather than as separate waves from the primary tumor
- Tumor cells sharing a common heritage travel from one site to another and retain their genetic imprint
- Supports “seed and soil” theory where subclones develop the potential to metastasize in the primary tumor, rather than being a property of the primary tumor as a whole



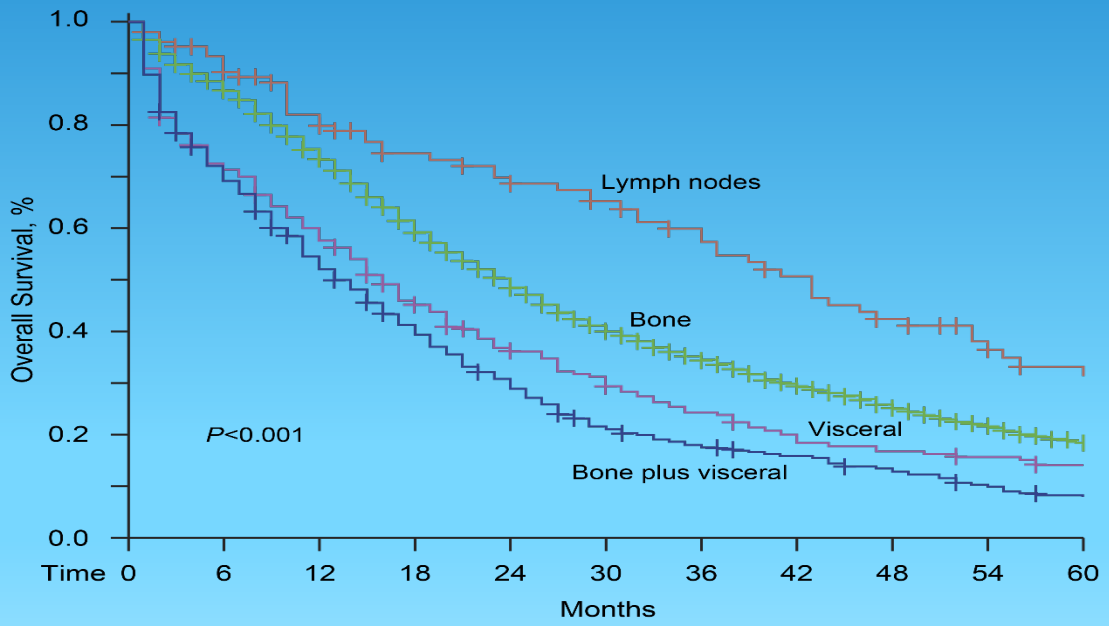
A – L humerus BM
D – Seminal vesicle
C – Prostate
E – L adrenal
F – R adrenal
G – Bladder
H – Pelvic LN
I – L pelvic LN
J – R pelvic LN
K – L pelvic LN
L – L media LN

BM, bone marrow; LN, lymph node.
Gundem G et al. *Nature*. 2015;520(7547):353-357.

Progression From Bone to Multiple Metastatic Sites Decreases Survival in CRPC

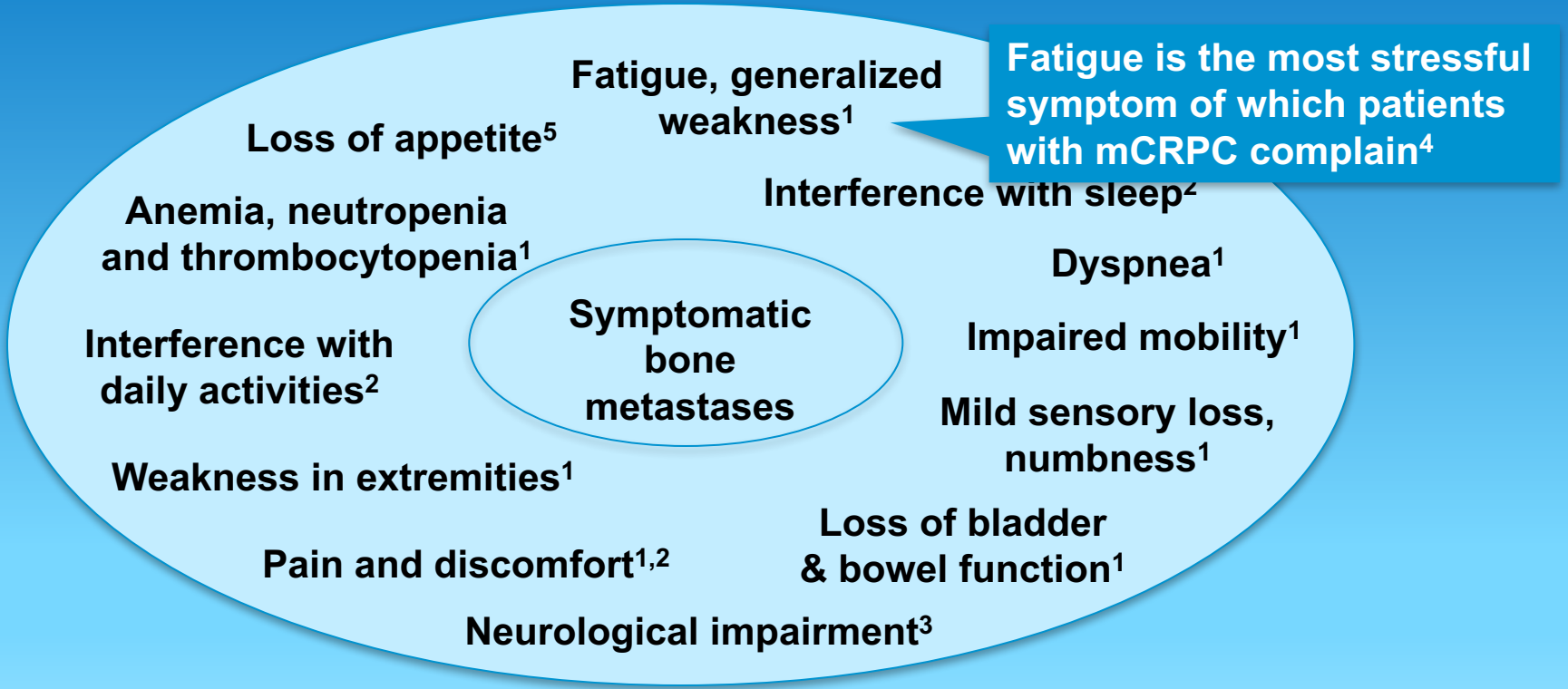
- Mortality increases as the disease progresses from lymph nodes to bone to visceral tissue
- Bone plus visceral metastases has the worst prognosis
- The site of metastases may have prognostic implications

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)



Gandaglia G et al. *Eur Urol*. 2015;68(2):325-334.

Multiple Symptoms Are Associated With Bone Metastases



1. Farrell C. *Br J Nurs*. 2013;22(10):S4-S11. 2. Autio KA et al. *J Oncol Pract*. 2013;9(5):223-229. 3. Selvaggi G et al. *Crit Rev Oncol Hematol*. 2005;56(3):365-378. 4. Colloca G et al. *Clin Genitourin Cancer*. 2016;14(1):5-11. 5. Hamilton W et al. *Br J Gen Pract*. 2015;65(637):e516-522.

Nearly 7 of 10 Patients (68%) Ignore Their Symptoms[1]

- Health care professionals need to focus on, and be more proactive with, discussing symptoms with patients because symptoms are being routinely underreported
- The most common advanced prostate cancer symptoms reported by men with bone metastases in the US include
  - 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%[2]
  - Loss of appetite: 20%[2]

1. Bayer. MenWhoSpeakUp. http://www.menwhospeakup.com/index.php. Accessed July 2015. Prostate Cancer Symptoms Survey: US Results, 2015. 2. Hamilton W et al. *Br J Gen Pract*. 2015;65(637):e516-522.

Detection of Metastatic Disease

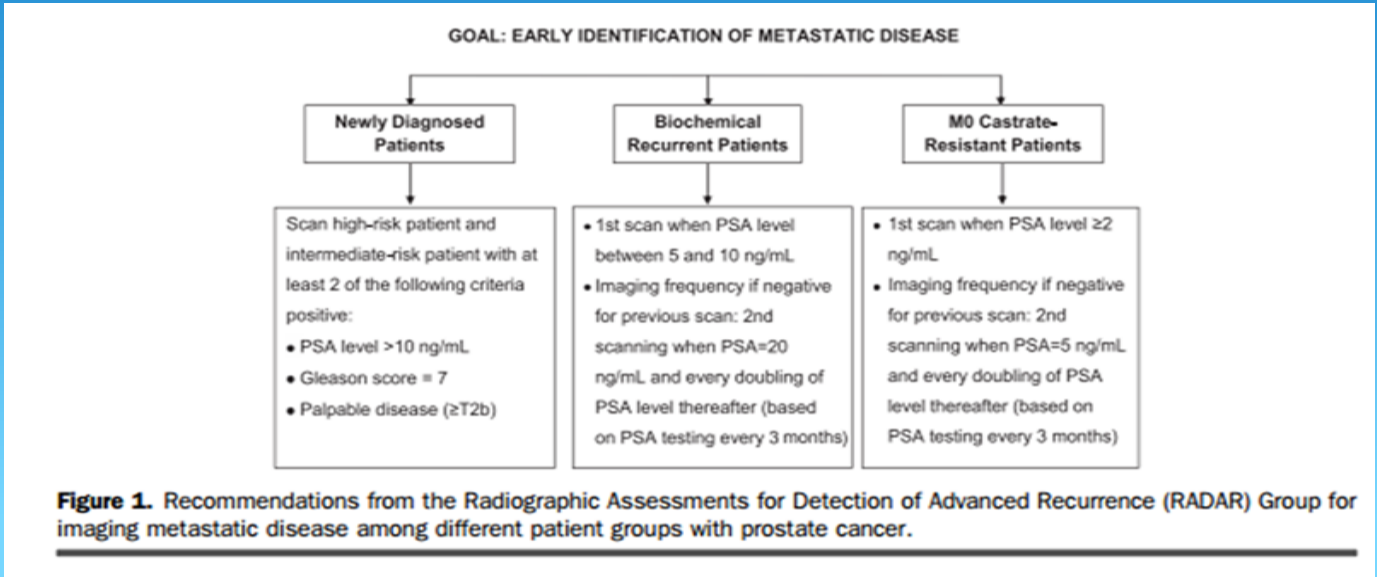


Figure 1. Recommendations from the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group for imaging metastatic disease among different patient groups with prostate cancer.

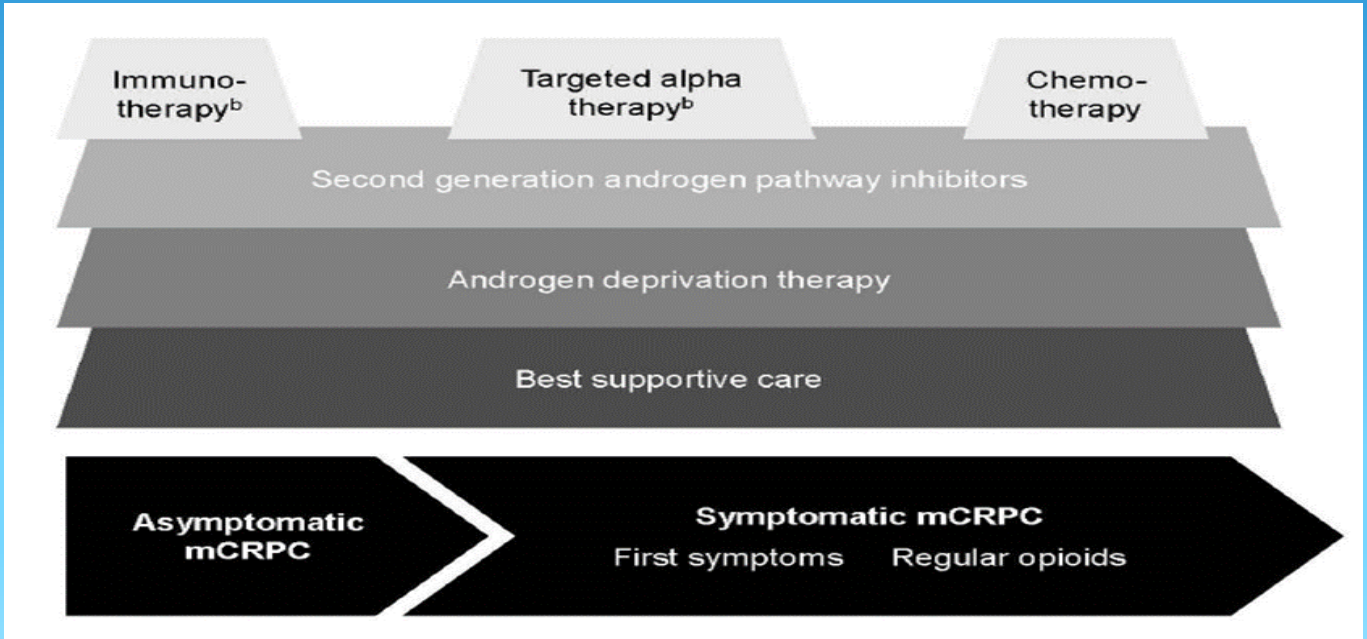
NaF
PSMA

Fluciclovine
Choline
NaF

FDG

Layer

Therapeutic Layering



Right Patient/Right Time

- “Layer” radium 223 on top of 2nd generation androgen inhibitor when PSA rises
- Bone mets
- Signs and symptoms (fatigue, impaired mobility, pain, etc.)
- Improved results with 5-6 doses
- More likely to receive all 6 when treated earlier

Optimizing Radium Therapy

- Commitment to completing therapy

Complete Therapy

- Patients with less prior therapy completed more cycles
- Clinical parameters which reflect earlier disease stage were associated with therapy completion.
- Concurrent abiraterone and previous sip-T associated with 5-6 therapies

Sartor. ASCO 2015
McKay RR, et al. Clin Genit cancer. 2016

Overall Survival Benefit

- Total radium cycles and abiraterone assoc with OS, PFS, and BeFS
- Higher mortality in patients in the group of patients receiving < 5 doses vs. > 5 doses (51% vs 30%).

Etcheberre, et al. EJNMMI 2015.
Taplin, et al. ASCO 2015.

- Well tolerated
- OS may be longer in patients receiving:
  - Radium 223 + abiraterone
  - Radium 223 + denosumab

Imaging

- Imaging is one way to assess for progression, not the only way

Progression

- Convincing and consistent rise in PSA
- Radiographic progression
- Clinical symptoms while on therapy

APPC recommendations

	Biomarker	Baseline (pre-tx)	3 mo	6 mo	FU	Comment
Assess at each scheduled visit	Clinical symptoms	+	+	+	+	
	Total ALP	+	+	+	+	Bone-specific ALP is being investigated as a marker of disease progression
	LDH	+	+	+	+	Regular measures of LDH may be useful in the interpretation of discordant results1
	Hematologic parameters	+	+	+	+	Routine monthly controls before each cycle
	PSA	+	(+)	(+)	+	Uncertainties exist in the interpretation of PSA for radium-223, and PSA should not by itself drive the decision for treatment discontinuation1
Assess as clinically indicated	Bone scan	+	–	(+)	+	A bone flare may be observed during the first months of treatment and should not be interpreted as progression2
	CT scan	+	–	–	(+)	Uncertainty exists in the frequency of CT scan use for radium-223. The APCCC recommends a frequency of every 2–4 months, 6 months, or only if clinically indicated

APCCC, Advanced Prostate Cancer Consensus Conference; (+) recommended; (+) to be considered; (–) not routinely recommended.
SOURCES: 1) Gillessen S, et al. Ann Oncol 2015;26(8):1589–1604. 2) Omlin AG, et al. J Clin Oncol 2016;34(suppl; abstr 5057).

Changes in Management

- Carefully consider mechanism of action of the therapeutic agent
- PSA progression: Reimage and alter/layer

Summary

- Identify the right patient
- Layer at the right time
- Commit