



MMRF

**Multiple Myeloma
Research Foundation**

Funding treatments faster. Finding a cure.

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June 13, 2008

Dear Colleague,

Welcome to New Orleans and to the **Clinical Imaging in the Diagnosis and Treatment of Multiple Myeloma** roundtable sponsored by the Multiple Myeloma Research Foundation (MMRF). This roundtable provides the opportunity for leading experts in the myeloma and radiology fields to discuss the current role of clinical imaging to monitor diagnosis, progression, and treatment of multiple myeloma; and to identify gaps in the ability to use existing imaging technologies more effectively. Furthermore, the participants will explore the potential of applying future imaging innovations to myeloma.

The two co-chairs of this roundtable, Sundar Jagannath, MD, from St. Vincent's Comprehensive Cancer Center and Ronald C. Walker, MD, FACNP, from Vanderbilt University Cancer Center have assembled a distinguished group of speakers and participants from academia and industry. Collectively we will engage in an open and stimulating discussion that will challenge our current thinking, increase our knowledge, and identify key questions and gaps in the use of imaging to treat this disease. The MMRF will use the information from this roundtable to develop a Request for Applications (RFA) designed to advance the use of existing as well as future clinical imaging technologies in the diagnosis and treatment of myeloma.

The MMRF would like to take the opportunity to thank GE Healthcare for its generous support of this roundtable.

Once again, thank you for joining us. We look forward to working together today and in future endeavors.

Sincerely,

Joan B. Levy, PhD
Associate Director of Research
Multiple Myeloma Research Foundation
Norwalk, CT

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AGENDA

Co-Chair

Sundar Jagannath, MD
*Chief, Multiple Myeloma Program
Bone Marrow and Blood Stem Cell Transplantation
St. Vincent's Comprehensive Cancer Center
New York, NY*

Co-Chair

Ronald C. Walker, MD, FACNP
*Associate Professor of Radiology and
Radiological Sciences
Vanderbilt University Medical Center
Nashville, TN*

Objectives:

- To understand the current role of clinical imaging to monitor myeloma diagnosis, progression, and response to treatment
- To identify possible gaps in our ability to use existing imaging technology in both diagnosis and treatment of multiple myeloma
- To explore the potential of future imaging innovations in myeloma
- To develop a Request for Applications (RFA) designed to advance the use of existing as well as future clinical imaging in myeloma

1:00 PM **Light Lunch**

2:00 PM **Introduction and Objectives**
*Louise M. Perkins, PhD
Multiple Myeloma Research Foundation*

2:15 PM **Session I – Multiple Myeloma Overview**
Session Moderator: Sundar Jagannath, MD

Myeloma and Bone Biology
*Noopur S. Raje, MD
Massachusetts General Hospital*

The Current State of Diagnosis and Treatment of Myeloma
*Sundar Jagannath, MD
St. Vincent's Comprehensive Cancer Center*





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An MMRF Roundtable

June 13, 2008

2:55 PM **Session II – The Current Role of Clinical Imaging to Monitor Myeloma
Diagnosis, Progression, and Response to Treatment**
Session Moderator: Ronald C. Walker, MD, FACNP

Overview

*Ronald C. Walker, MD, FACNP
Vanderbilt University Medical Center*

PET/CT

*Homer A. Macapinlac, MD
The University of Texas
M.D. Anderson Cancer Center*

MRI

*Jon Jacobson, MD
University of Michigan*

4:00 PM **Break**

4:15 PM **Session III – Discussion: Identifying Gaps in Existing Imaging
Technology in Myeloma**
Session Moderators: Sundar Jagannath, MD, and Ronald C. Walker, MD, FACNP

5:00 PM **Session IV – The Potential of Future Imaging Innovations**
*Session Moderator: Ora Israel, MD
Rambam Health Care Campus*

*Steve Larson, MD
Memorial Sloan-Kettering Cancer Center*

*Richard L. Wahl, MD, FACR
Johns Hopkins Medical Center*

*Jean Luc Vanderheyden, PhD
GE Healthcare*

6:15 PM **Wrap-up and Next Steps**
*Joan B. Levy, PhD
Multiple Myeloma Research Foundation*

7:00 PM **Conclusion**

7:30 PM **Departure for Off-site Dinner**



CO-CHAIR BIOGRAPHIES

Sundar Jagannath, MD

*Chief, Multiple Myeloma and Stem Cell Transplant Program
St. Vincent's Comprehensive Cancer Center
New York, NY*

Dr. Jagannath is Chief of the Multiple Myeloma Program and the Bone Marrow and Stem Cell Transplantation Program at St. Vincent's Comprehensive Cancer Center in New York City.

Dr. Jagannath has received numerous awards in honor of his study and treatment of myeloma. He is Editor-in-Chief of *Clinical Lymphoma & Myeloma* and a peer reviewer for many other medical journals. Dr. Jagannath is an active member of the American College of Physicians, the American Society of Clinical Oncology, and the American Society of Hematology.

Ronald C. Walker, MD, FACNP

*Associate Clinical Professor of Radiology and
Radiological Sciences
Vanderbilt University Medical Center
Nashville, TN*

Dr. Walker is an Associate Clinical Professor of Radiology and Radiological Sciences at the Vanderbilt University Medical Center and a Staff Radiologist/Nuclear Medicine Physician in the Department of Radiology/Nuclear Medicine of Vanderbilt University Medical Center and the Tennessee Valley VA Healthcare System in Nashville.

Dr. Walker is an elected fellow of the American College of Nuclear Physicians. He holds a U.S. patent regarding the use of fluorine-18-labeled fluoroquinolone antibiotics for diagnosing and monitoring bacterial infection. Dr. Walker serves as a reviewer for many journals including the *American Journal of Roentgenology* and the *Journal of Magnetic Resonance Imaging*. He is an active member of the Society of Nuclear Medicine, the Radiological Society of North America, and the American College of Radiology.



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ABSTRACTS

Myeloma and Bone Biology

Noopur Raje, MD

The bone marrow (BM) microenvironment plays a crucial role in multiple myeloma (MM) cell pathogenesis. Specifically, growth advantage, survival, and drug resistance of MM cells can be modulated by various subsets of BM cell components including BM stromal cells, osteoclasts, osteoblasts, and vascular endothelial cells. Osteolytic bone lesions are a common feature of MM and result in bone pain, hypercalcemia, pathologic fractures, and reduced function. Vertebral collapse, along with the associated effects of a tumor mass, results in back pain, kyphosis, and height loss, as well as root and cord compressive events including paraparesis. This is often the most disabling complication of MM bone disease. Normal bone physiology is a dynamic process involving a balance between bone formation and resorption. In MM, an alteration in bone homeostasis occurs, tilting the balance toward excessive bone resorption because of increased osteoclastic activity. The result is osteolytic bone disease. At the same time, osteoblasts are markedly suppressed and very little, if any, osteoblastic activity is noted. Increased osteolytic activity results in a BM niche favorable to tumor growth, proliferation, survival, and drug resistance. The tumor cell, in turn, produces soluble factors including interleukin (IL)-1 β , IL-6, lymphotoxin, tumor necrosis factor- α , macrophage inflammatory protein-1 α , and the ligand for the receptor activator of nuclear factor- κ B (RANKL). Other factors, such as dickkopf-1 (DKK1), a negative regulator of the Wnt signaling cascade and a target of the β -catenin/T-cell factor pathway, have been shown to correlate with bone disease and inhibit osteoblastogenesis. Thus, understanding the regulation of these interactions may provide important insights into developing therapeutic tools to target these pathways.



ABSTRACTS

The Current Role of Clinical Imaging to Monitor Myeloma Diagnosis, Progression, and Response to Treatment

Ronald C. Walker, MD, FACNP

Focal lesions (FL) of bone on x-rays that lead to focal osteolytic (OL) lesions of bone that never heal are a hallmark of multiple myeloma (MM), incorporated into the original DS Staging system (Durie and Salmon, *Cancer* 1975). Imaging advances, specifically computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT have further defined both the imaging role and the understanding of the disease.

The number of MRI-defined FL of bone at baseline correlates inversely with long-term prognosis, second only to clinically significant cytogenetic abnormalities (CA) in adverse impact. MM demonstrates marked genomic instability and heterogeneity, with higher yields of important CA coming from MRI-defined or PET/CT-defined FL than random marrow biopsies in the same patients. Investigations of the marrow microenvironment comparing patients with and without FL demonstrate a strong correlation between marrow levels of the enzyme dickkopf 1 (DKK1) and the number of FL at baseline, though the etiology for this relationship remains unclear.

FL on MRI or PET/CT ultimately lead to focal OL lesions if not successfully treated. The mechanism leading to focal aggregates of MM cells is unknown. There is usually a diffuse marrow infiltration of tumor in patients with FL on MRI or PET/CT, as well, which may or may not contribute to the systemic osteoporosis observed in this disease, responsible for much of the morbidity via insufficiency fractures. Indeed, some patients demonstrate diffuse infiltration alone with no FL. Finally, while uncommon, MM can be associated with diffuse osteosclerosis with or without associated focal osteolytic bone lesions.

Extramedullary disease (EMD), originally thought rare at diagnosis, is seen more commonly with whole body imaging techniques, such as CT and PET/CT. Since many therapeutic agents exploit the MM/marrow microenvironment interaction, the presence of EMD implies a tumor entity resistant to such treatments in a high-risk patient in need of close follow-up and aggressive treatment.



ABSTRACTS

The Potential of Future Imaging Innovations

Steven Larson, MD

Multiple myeloma may involve multiple organ systems, particularly bone and bone marrow with growing malignant plasma cells, and organs (such as heart and kidney) with deposition of amyloid in amounts which can interfere with function.

In regard to bone and bone marrow involvement, it is a challenge to categorize response to therapy, because conventional methods such as computed tomography (CT) are useful for identifying the extent of past involvement but may not be useful for assessing the current status of active disease. Similarly, bone scanning may be useful in defining progression of disease, but is less useful in documenting response. Magnetic resonance imaging (MRI) may also be useful, especially in the spine, and gives a highly sensitive record¹ of the extent of bone involvement but the difficulty of interpretation of the study lies in discerning which sites in bone are metabolically active.

Positron emission tomography – [18F]-2-fluoro-deoxy-D-glucose (PET-FDG) imaging, using quantitative imaging methods has the potential to assess activity of disease in bone and bone marrow,² but may be prone to interference from bone marrow activity, especially in treated patients, and is more easily interpreted when the disease is diffuse rather than focal in bone marrow.³ A comparison of MRI and FDG-PET has shown comparable sensitivity for detecting focal tumors, although MRI may be more useful in diffuse disease.⁴

In the future, fluoride F-18 bone scans offer attractive quantitative features for imaging of myeloma in comparison with conventional bone scanning.⁵ Clearly, alternative imaging agents beyond FDG may be useful in identifying both bone and extramedullary lesions, and in a small recent study, 11C choline identified more active lesions with higher standardized uptake values (SUVs).⁶ 11C-methionine also showed high SUVs in active tumor in comparison with bone marrow and detected extramedullary sites.⁷ Clearly, the addition of more specific agents, such as antibodies⁸ labeled with positron emitters may be useful in detecting disease extent.

Deposition of amyloid in the heart is an important cause of cardiac insufficiency in these patients and there may be an opportunity to study this with novel imaging agents such as 11C-PIB (Pittsburgh Compound B), an agent which has been used in Alzheimer's disease to document brain amyloid.^{9,10} In principle, this tool could also be used to study renal changes as well. Backing this up with functional imaging approaches in the heart would include assessment of other aspects of cardiac integrity, such as innervation in the heart, with I-123 and I-124 metaiodobenzylguanidine (MIBG), perfusion in the heart, with rubidium-82 (Rb82) or technetium-99m (Tc99m sestamibi), and cardiac function with Multiple Uptake Gated Acquisition (MUGA) scanning.

1. Hur J, Yoon CS, Ryu YH, Yun MJ, Suh JS. Comparative study of fluorodeoxyglucose positron emission tomography and magnetic resonance imaging for the detection of spinal bone marrow infiltration in untreated patients with multiple myeloma. *Acta Radiol.* 2008;49(4):427-435.
2. el-Shirbiny AM, Yeung H, Imbriaco M, Michaeli J, Macapinlac H, Larson SM. Technetium-99m-MIBI versus fluorine-18-FDG in diffuse multiple myeloma. *J Nucl Med.* 1997;38(8):1208-1210.
3. Even-Sapir E. PET/CT in malignant bone disease. *Semin Musculoskelet Radiol.* 2007;11(4):312-321.



ABSTRACTS

The Potential of Future Imaging Innovations (CONT)

Steven Larson, MD

4. Fonti R, Salvatore B, Quarantelli M, et al. 18F-FDG PET/CT, 99mTc-MIBI, and MRI in evaluation of patients with multiple myeloma. *J Nucl Med.* 2008;49(2):195-200.
5. Even-Sapir E, Mishani E, Flusser G, Metser U. 18F-Fluoride positron emission tomography and positron emission tomography/computed tomography. *Semin Nucl Med.* 2007;37(6):462-469.
6. Nanni C, Zamagni E, Cavo M, et al. 11C-choline vs. 18F-FDG PET/CT in assessing bone involvement in patients with multiple myeloma. *World J Surg Oncol.* 2007;5:68.
7. Dankerl A, Liebisch P, Glatting G, et al. Multiple Myeloma: Molecular Imaging with 11C-Methionine PET/CT—Initial Experience. *Radiology.* 2007;242(2):498-508.
8. Sun J, Li Y, Sun Y, Yu M, Feng J, Shen B. Preparation and characterization of a monoclonal antibody against human B lymphocyte stimulator. *Hybridoma (Larchmt).* 2006;25(2):80-85.
9. Jack CR, Jr., Lowe VJ, Senjem ML, et al. 11C PIB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain.* 2008;131(Pt 3):665-680.
10. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain.* 2007;130(Pt 11):2837-2844.



ABSTRACTS

The Potential of Future Imaging Innovations

Jon Jacobson, MD

The purpose of this presentation is to review the role of magnetic resonance imaging (MRI) in the evaluation of myeloma. Initial general comments will include the advantages and disadvantages of MRI compared with other imaging methods such as radiography and computed tomography (CT). A review of current MRI sequences used to evaluate bone marrow will follow. Current applications of MRI in myeloma will be discussed, including detection, staging, prognosis, and response, as well as evaluation for vertebral body fracture and avascular necrosis. Examples of MRI staging of myeloma (Durie-Salmon PLUS) will include diffuse and focal disease of the spine and pelvis. A brief discussion of problems and challenges will include topics such as whole body MRI, nonspecificity of MRI, nephrogenic systemic fibrosis, and differentiating hematopoietic marrow from myeloma.

