18F-NaF PET/CT versus 99mTc-MDP for Detecting Bone Metastases:

A Randomized, Multi-center Trial to Compare 2 Bone Imaging Techniques

Martin Auerbach, MD
Ahmanson Biological Imaging Division
David Geffen School of Medicine at UCLA

Background I

- 1.9 Million conventional bone scans/year*

- Limitations of conventional bone scanning

- 18F-NaF PET/CT imaging is equal or superior to current technology for the detection of bone metastases

- Tc^{99m} shortage

*Source: BioTech report:

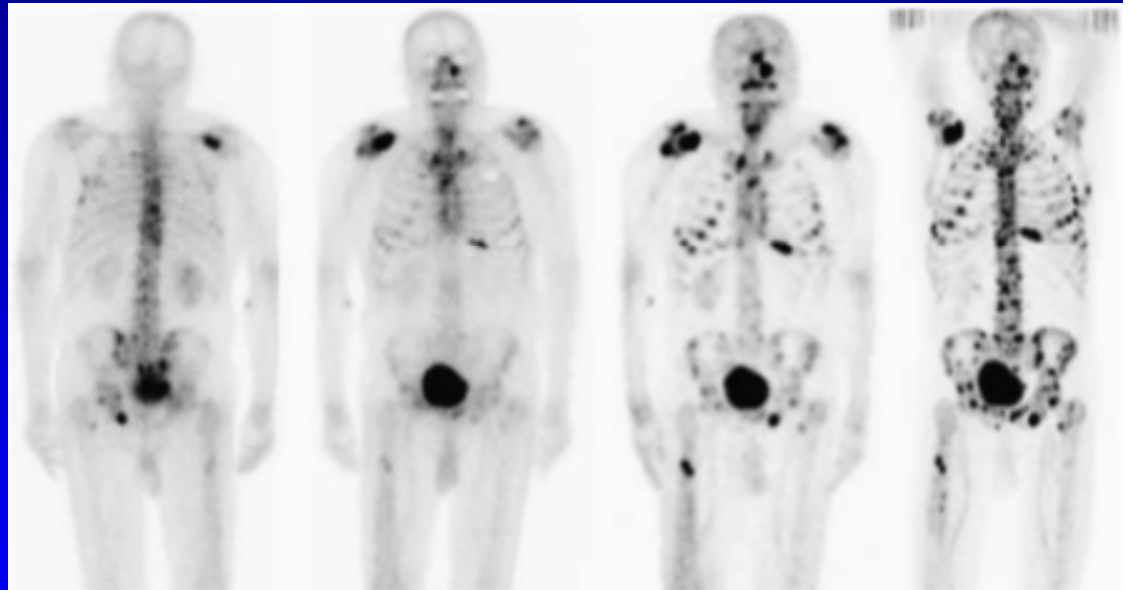US market for PET and SPECT radiopharmaceuticals 2009
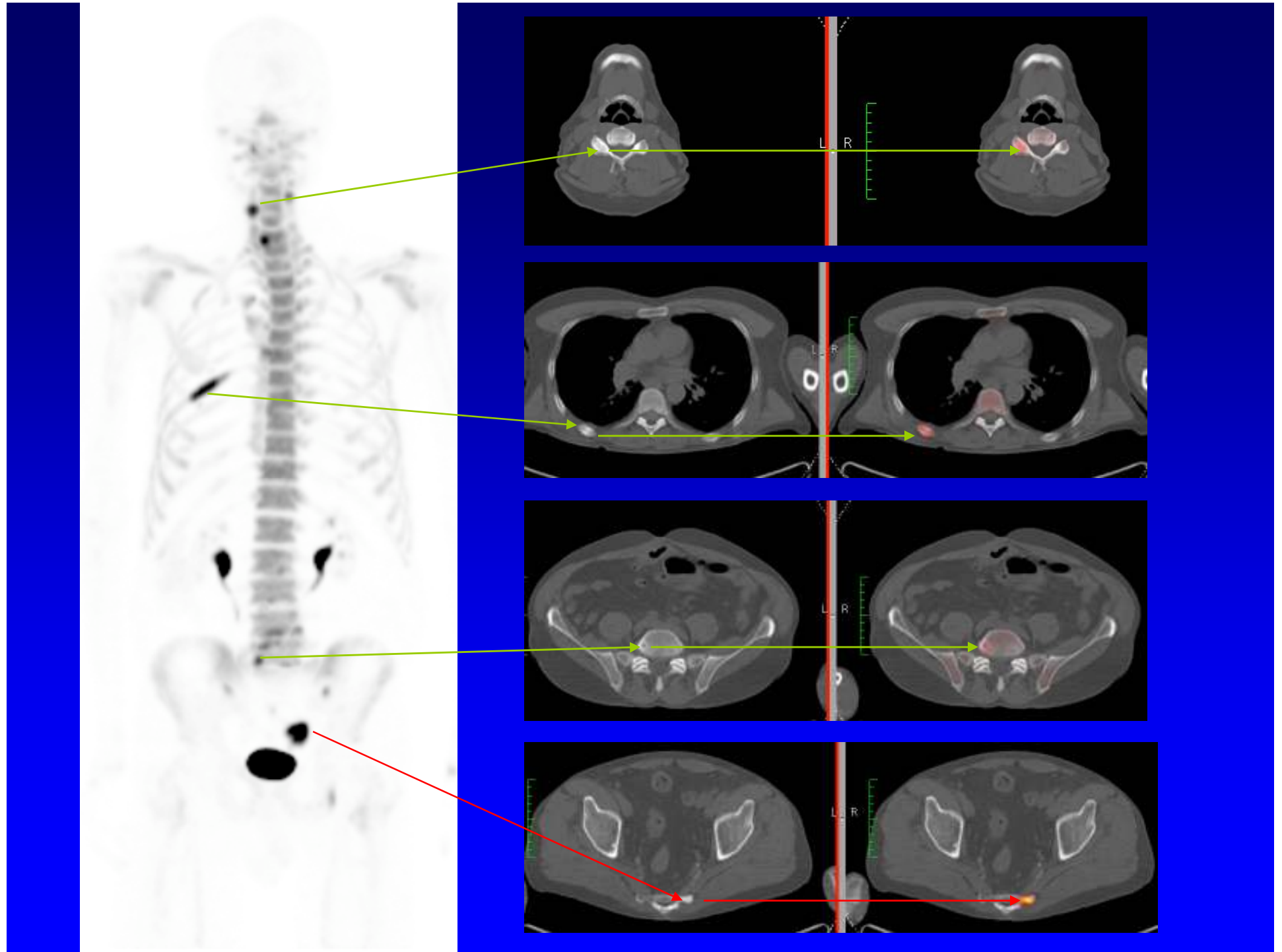
AMII
ACADEMY OF MOLECULAR IMAGING

Background II
Why 18F-NaF PET/CT bone scans?

- Improved Sensitivity
  - PET often demonstrates lesions missed on planar bone scans

- Improved Specificity
  - greater ability to differentiate benign from malignant lesions

Even-Sapir et al, J Nucl Med 2006; 47:287–297

Trial Objectives

- Primary:
  - Compare diagnostic performance of 18F NaF PET/CT to conventional bone scanning for the detection of bone metastasis

- Secondary:
  - Determine the number of equivocal tests from each modality
  - Determine the impact of each modality on patient management (i.e. number of additional tests, change in management)
  - Report the number of adverse events reported with the use of 18F NaF

Study Design

- Open label, randomized, multi-center trial
- Eligibility
  - ≥ stage 3 breast cancer
  - ≥ stage 3 lung cancer
  - ≥ stage 2 prostate cancer and/or PSA> 10 ng/ml
- Off-site randomization: Image Metrix
- Image analysis: Core Lab
- Reference standard: Truth Panel after 12 months

AMI
ACADEMY OF MOLECULAR IMAGING

Primary Objective: Truth Panel

- Hard criteria
  - Biopsy
  - Confirmation of index lesion with CT, MRI or plain film x-ray
  - Change from lytic to blastic lesions with treatment
- Soft criteria
  - typical appearance of multifocal disease
  - increased lesion number over time
  - bone lesions + symptoms
  - increasing serum AP, PSA, or decreasing levels in response to treatment
- 1 hard or 3 soft criteria considered positive

Statistical Considerations

- *Hypothesis: 18F-NaF PET/CT is superior to conventional bone imaging*

- ROC curve analysis

- Sample size assumptions: AUC for MDP=0.70; for NaF: 0.80; 25% positive for disease

- At 80% power and $p<0.05$, 488 patients needed (assuming some dropouts total aim 550 patients)

ACADEMY OF MOLECULAR IMAGING

Secondary Objectives: Questionnaires

- Pre- and Post scan questionnaires
- Modeled on NOPR
- Questions regarding management intent

Pre-Scan Questionnaire

PR

Pre-Scan Questionnaire (^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan)

|____| 1. Indicate your clinical suspicion for bone metastases (select one option from list)

      1) Low
      2) Moderate
      3) High (1)

|____| 2. Indicate your pre ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan working clinical summary staging (select one option from list)

      1) No evidence of disease/in remission
      2) Localized only
      3) Regional by direct extension or lymph node involvement or both
      4) Metastatic (distant) with single suspected site
      5) Metastatic (distant) with multiple suspected sites
      6) Unknown or uncertain (2)

|____| 3. Is a tissue biopsy planned?
      1) No
      2) Yes (3)

|____| 4. Indicate what your current management option would be if the ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan was not available (select one option from list) (4)

      1) Observation (with close follow up) (skip to Question # 5)
      2) Additional Imaging or other non-invasive diagnostic tests (Complete 4a, then skip to # 5)
      3) Treatment (includes surgical resection) (Skip 4a and Complete 4b and 4c)

          4a. Select the additional imaging or other non-invasive diagnostic tests (choose all that apply)

          |____| 1) X-Ray (5)

          |____| 2) CT (6)

          |____| 3) MRI (7)

          |____| 4) FDG-PET (8)

          |____| 5) Other (9) Specify (10):_____

Pre-Scan Questionnaire

|__|__| 4b. Select the Treatment Goal

        1) Curative
        2) Palliative (11)

|__|__| 4c. Select Planned Treatment Type (from option list) (12)

        1) Surgery
        2) Chemotherapy
        3) Radiation
        4) Supportive Care
        5) Other Specify:_____(13)_____

5. Does the patient have bone pain?

|__|__|
        1) No
        2) Yes (Complete Q 5a) (14)

        5a. Indicate how the bone pain will be managed (select one option from list)

|__|__|
        1) NSAIDS
        2) Extensive pain management, including opioids
        3) Radiation treatment
        4) Samarium or Strontium
        5) Chemotherapy
        6) Radiation and Chemotherapy(15)

Post-Scan Questionnaire

PQ

Post-Scan Questionnaire (^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan)

|___| 1. Considering the ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan results, indicate your clinical suspicion of bone metastases
  1) Low
  2) Moderate
  3) High (1)

|___| 2. Did the ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan show evidence of cancer activity that was not previously reported?
  1) No
  2) Yes (2)

|___| 3. Did the ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan enable you to avoid any test or procedures?
  1) No
  2) Yes (3)

|___| 4. Indicate your post ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan working clinical summary staging (select one option from list)
  1) No evidence of disease/in remission
  2) Localized only
  3) Regional by direct extension or lymph node involvement or both
  4) Metastatic (distant) with single suspected site
  5) Metastatic (distant) with multiple suspected sites
  6) Unknown or uncertain (4)

|___| 5. Is a tissue biopsy planned?
  1) No
  2) Yes (5)

|____| 6. Indicate your preferred current management option in light of the ^{18}F Fluoride PET/CT or ^{99m}Tc-MDP conventional bone scan findings (select one option from list) (6)

    1) Observation (with close follow up) (skip to Question # 7)
    2) Additional Imaging or other non-invasive diagnostic tests (Complete 6a, then skip to # 7)
    3) Treatment (includes surgical resection) (Skip 6a and Complete 6b and 6c)

    6a. Select additional imaging or other non-invasive diagnostic tests (choose all that apply)

        |____| 1) X-Ray (7)

        |____| 2) CT (8)

        |____| 3) MRI (9)

        |____| 4) FDG-PET (10)

        |____| 5) Other (11) Specify (12):_____

|____| 6b. Select Treatment Goal
        1) Curative
        2) Palliative (13)

|____| 6c. Select Planned Treatment Type (from option list) (14)
        1) Surgical
        2) Chemotherapy
        3) Radiation
        4) Supportive Care
        5) Other Specify:_____(15)_____

|____| 7. Does the patient have bone pain? (16)
        1) No
        2) Yes (Complete Q 7a)

|____| 7a. Indicate how the bone pain will be managed (select one option from list)
        1) NSAIDS
        2) Extensive pain management, including opioids
        3) Radiation treatment
        4) Samarium or Strontium
        5) Chemotherapy
        6) Radiation and Chemotherapy (17)

# Participating Sites

- **Total Number of Sites**: 22
  - UCLA, Los Angeles VA, Scottsdale Imaging, Dartmouth, St. Louis University Hospitals, Duke University, University of Texas-MD Anderson, Stanford University, University of Utah, PET-CT Center LINZ, University Hospital Zurich, John Cochran Veterans Admin, Cedar Sinai, NY Presbyterian-Weill Cornell, NY MedScan, University of Michigan Health System, University Hosp. Freiburg, University of Texas Southwestern Medical Ctr., SouthCoast Imaging Center, University Hospital Geneva, Front Range Cancer Center, Moffitt Cancer Center, University of Iowa, University North Carolina Healthcare, University New Mexico, Adler Institute for Advance Imaging, Mayo Clinic
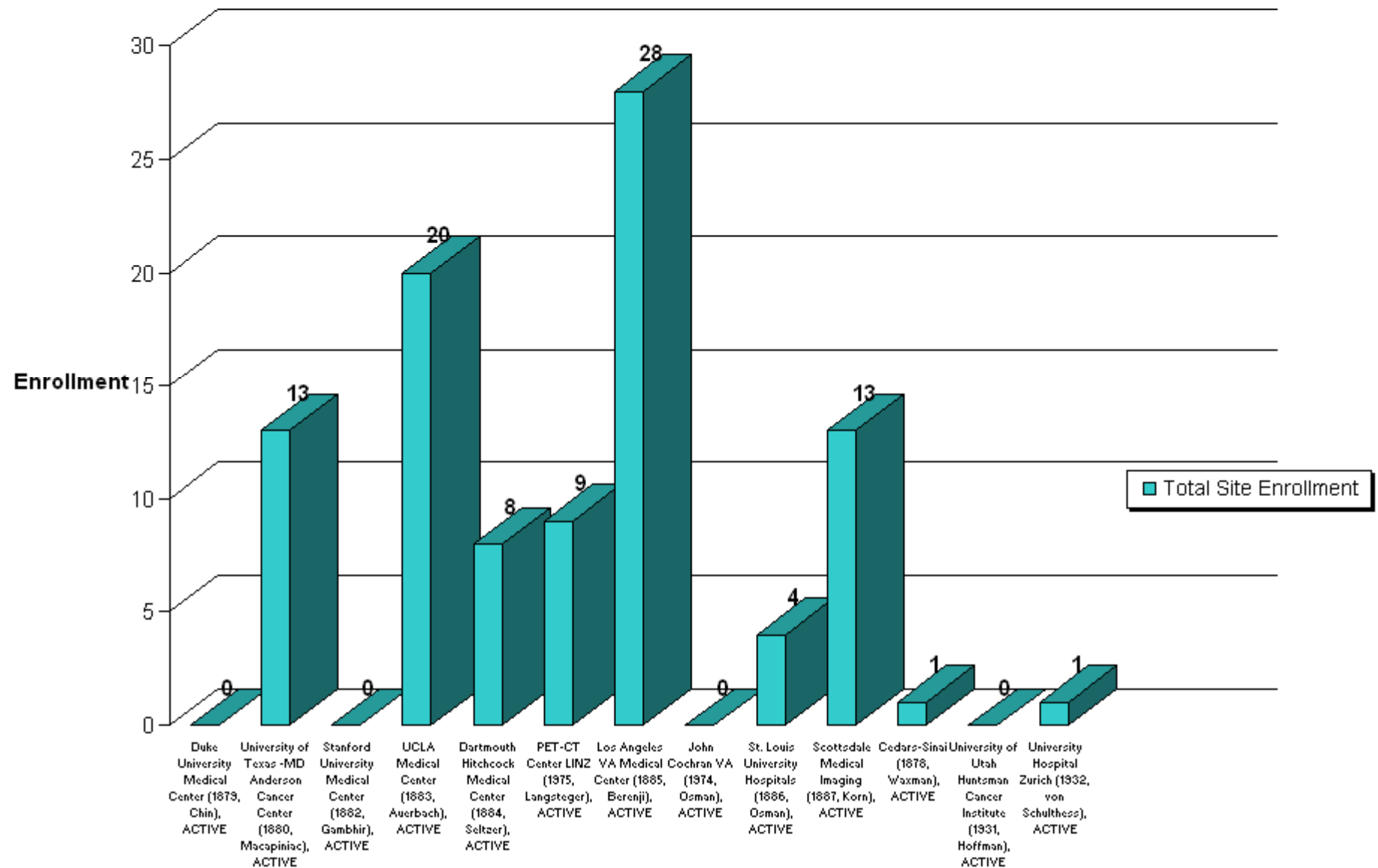
- **Active Recruiting Sites:** 13
  - UCLA, Los Angeles VA, Scottsdale Imaging, Dartmouth, St. Louis University Hospitals, Duke University, University of Texas-MD Anderson, Stanford University, University of Utah, PET-CT Center LINZ, University Hospital Zurich, John Cochran Veterans Admin, Cedar Sinai
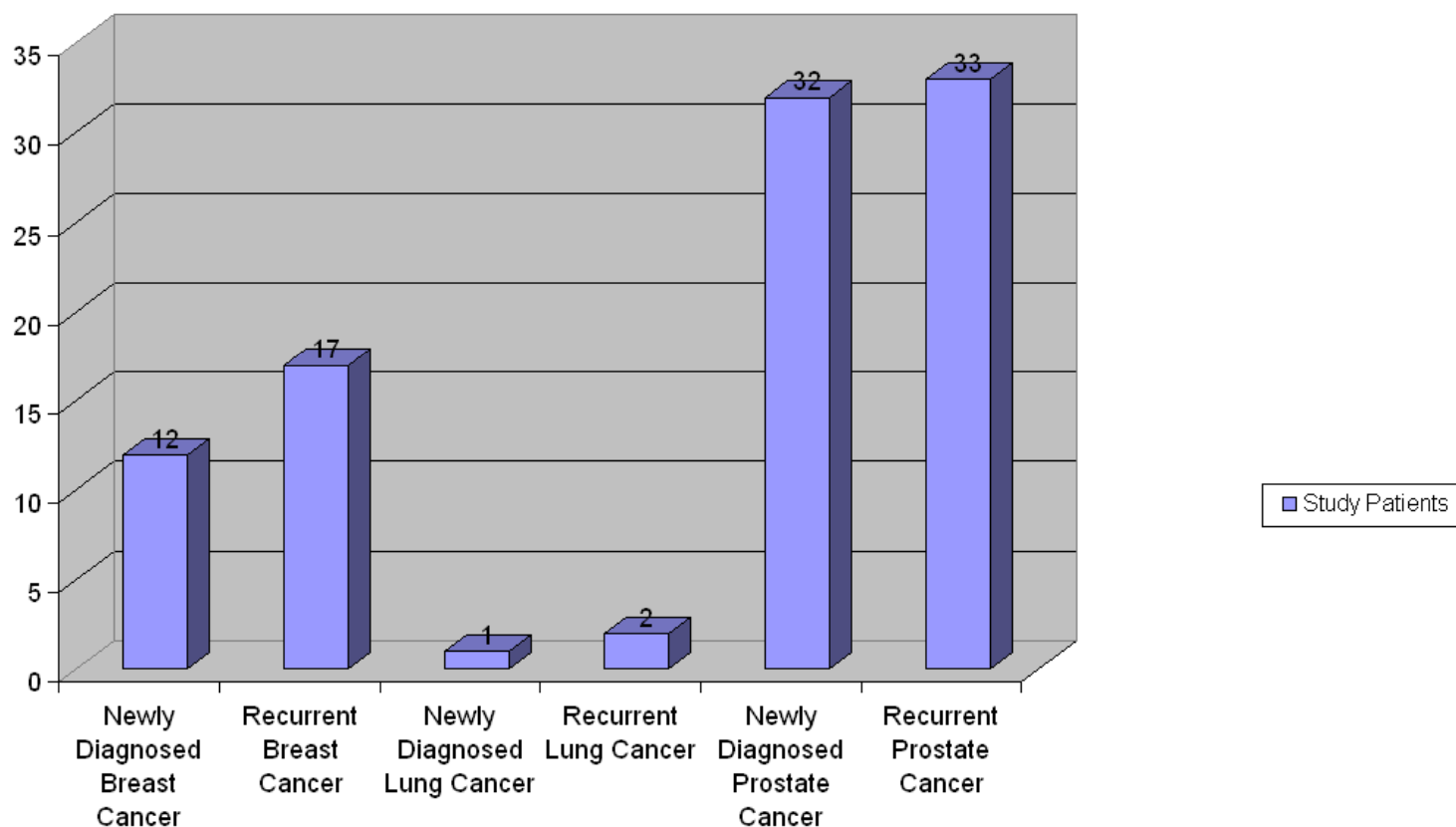
Enrollment Update
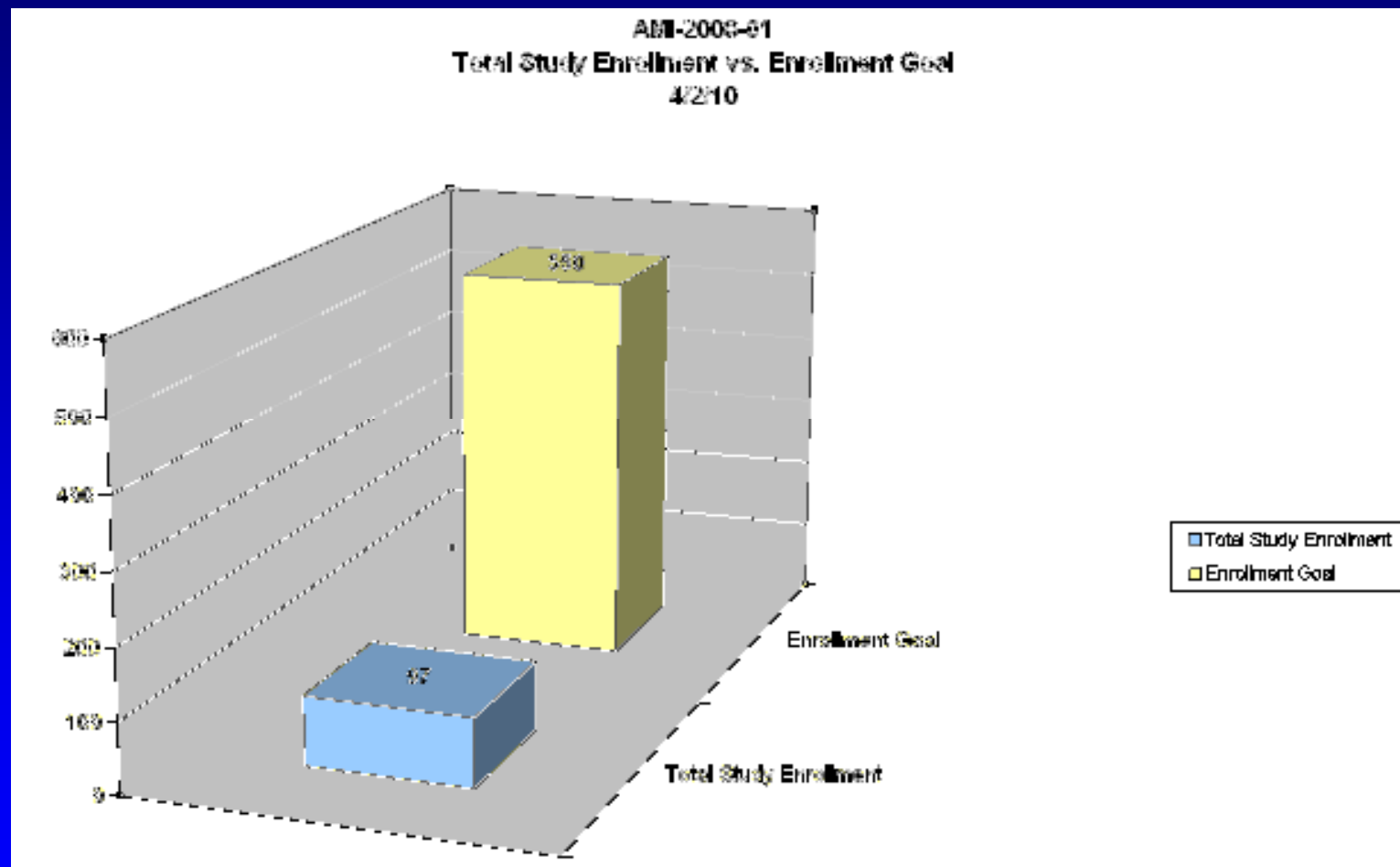
AMI-2008-01
Total Site Enrollment
4/2/10

Disease Distribution

AMI-2008-01
Total Enrollment by Indication
4/2/10

CMS NCD February 26, 2010

- CMS concluded that NaF-18 PET should be covered only under an approved coverage with evidence development (CED) study.

- At the present time, there is no qualifying clinical study for NaF-18 PET that would enable this coverage.

Concluding Thoughts

- Strong evidence that 18F-NaF PET is the best exam to identify bone metastasis

- AMI clinical trial will augment current clinical evidence in support of 18F-NaF PET

- NOPR is considering the development of a data registry for NaF-18 PET similar to that now in place for many uses of FDG-PET.

AMII
ACADEMY OF MOLECULAR IMAGING