Bone Scan Index as a Prognostic Biomarker

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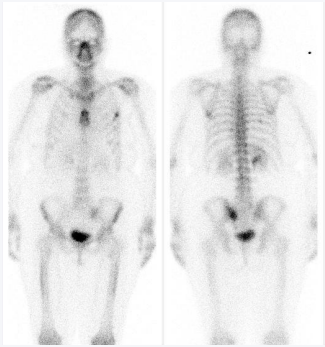
Imaging Biomarkers

- Biomarker (FDA-NIH definition)
  - A defined characteristic that is measured as an indicator of:
    - normal biological processes,
    - pathogenic processes, or
    - responses to an exposure or intervention including therapeutic interventions
  - Molecular, histologic, **radiographic** or physiologic characteristics are examples.
- Imaging Biomarker
  - A characteristic measured from a medical image

Imaging Biomarkers

- Imaging biomarker example
  - *Two or more new lesions on bone scan follow-up (PCWG)*



PCCTC Bone Scan Assessment Tool

8 Week Scan Date: (_____/_____/_____)

Patient Identifier:

Protocol Number: | Protocol Start Date:

Is tracer uptake related to metastatic disease?

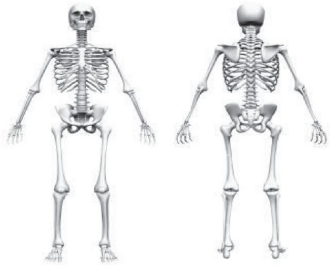
◯ Yes ◯ No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ Skull
- ❑ Thorax
- ❑ Spine
- ❑ Pelvis
- ❑ Extremities



If yes, indicate total number of NEW lesions compared to Baseline Scan (Date:___/___/___)

(select one)

◯0 ◯1 ◯2 ◯3 ◯4 ◯5 ◯>5

*Presence of new lesions at this time does not confirm progression *

Clinical Impression (circle one)

◯ Improved ◯ Stable ◯ Progression

Comments		Investigator's Signature	

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PCCTC Bone Scan Assessment Tool

Assessment Worksheet

Patient Identifier:

Protocol Number: | Protocol Start Date:

Date of Scan: _____ / _____ /_____

1. Are there 2 or more new lesions compared to the WEEK 8 SCAN?

◯ Yes ◯ No

If YES, proceed to question 2.

If NO, the patient does not have radiographic progression by bone scan.

2. Is this the first scan performed POST the WEEK 8 SCAN?

◯ Yes ◯ No

If YES, proceed to question 3A. If NO, proceed to question 3B.

3A. Were there 2 or more new lesions at the WEEK 8 SCAN compared to the BASELINE SCAN?	3B. Does this scan confirm the presence of 2 or more new lesions seen since the WEEK 8 SCAN?
◯ Yes ◯ No	◯ Yes ◯ No

If YES, patient has met conditions for radiographic progression by bone scan.

If NO, the patient does not have radiographic progression by bone scan.

Comments		Investigator's Signature	

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Imaging Biomarkers

CONSENSUS

OPEN

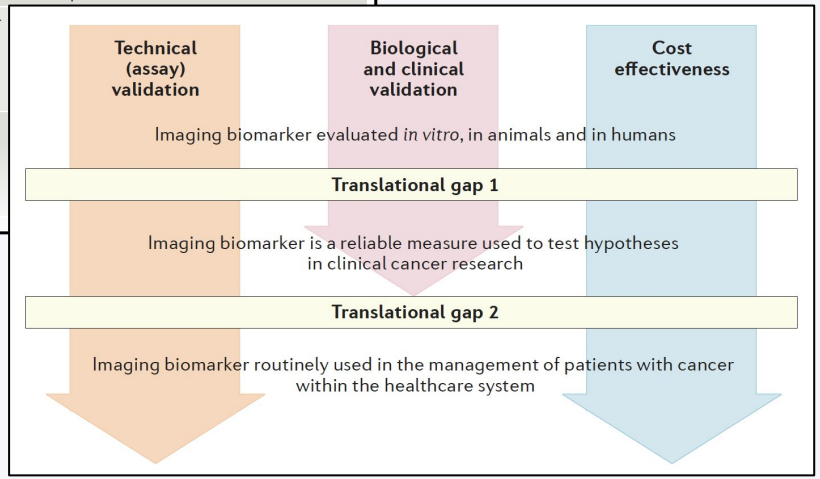
Imaging biomarker roadn
cancer studies

James P. B. O'Connor[1], Eric O. Aboagye[2], Judith E. Adams[3],
Sally F. Barrington[5], Ambros J. Beer[6], Ronald Boellaard[7], Sc
Michael Brady[9], Gina Brown[10], David L. Buckley[11], Thomas

Clinical Oncology March 2

Table 1 | **Selected list of imaging biomarkers used in clinical oncology decision-making**

Biomarker	Modality	Decision-making role	Notes	Refs
IBs that have crossed translational gap 2 into healthcare				
ACR BI-RADS breast morphology	Mammography	Diagnostic in breast cancer	Used worldwide	42
Clinical TNM stage	XR, CT, MRI, PET, SPECT, US, endoscopy	Prognostic in nearly all cancers	• Used worldwide • Guides management of nearly every patient with a solid tumour • Extensively validated and qualified	43
Bone scan index	SPECT	Prognostic in prostate cancer		
Left ventricular ejection fraction	Scintigraphy, US	• Safety biomarker • Guides therapy		



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In This Talk

- Computer aided diagnosis systems
  - Nice or need to have?
- **Established**
  - Bone Scan Index as a prognostic imaging biomarker
- **Up and coming**
  - Automated characterization of PSMA SPECT/CT images

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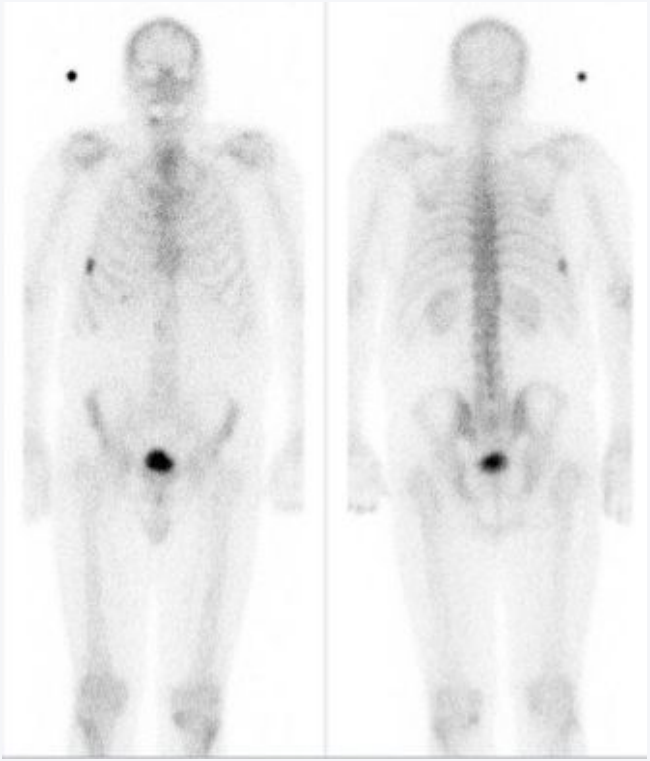
Image Interpretation is Variable



What is the likelihood of at least one metastasis?

53 physicians interpreting 5 bone scans

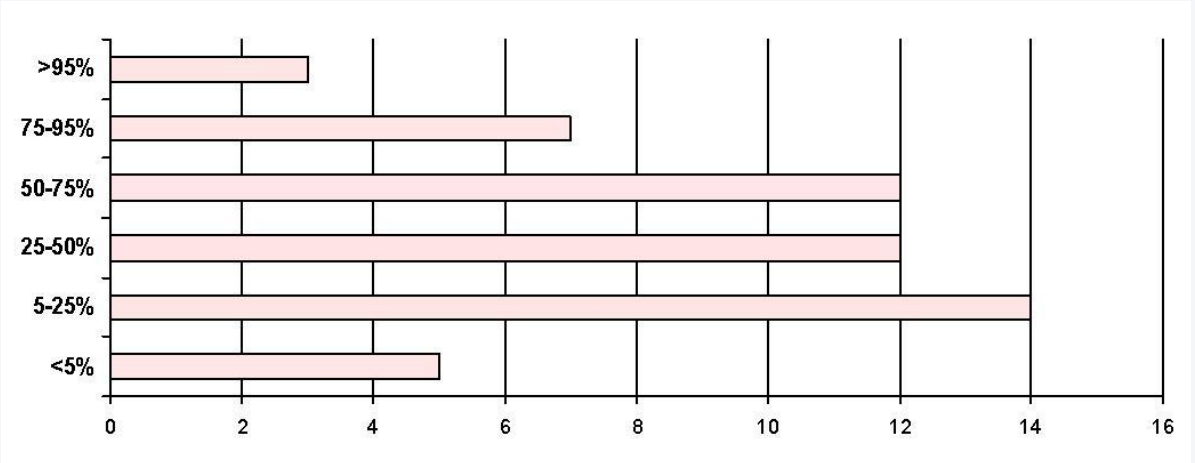


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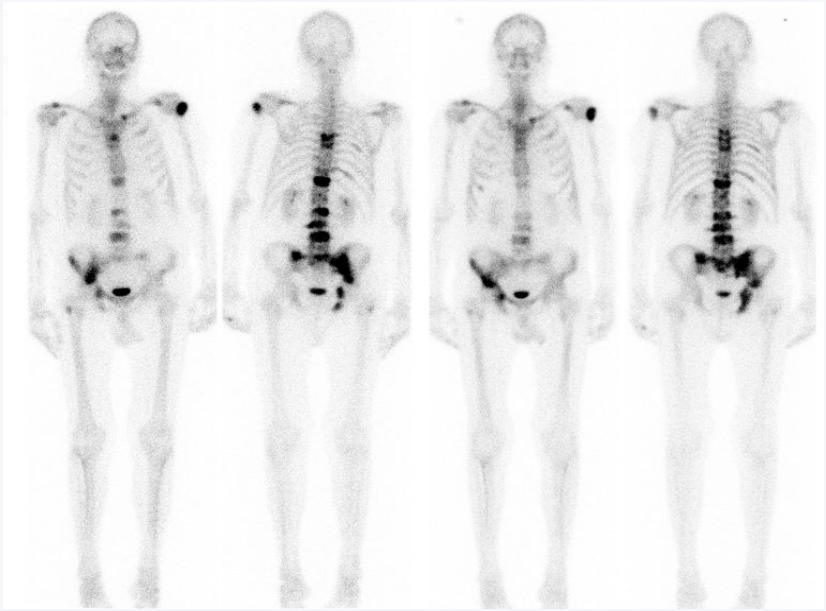
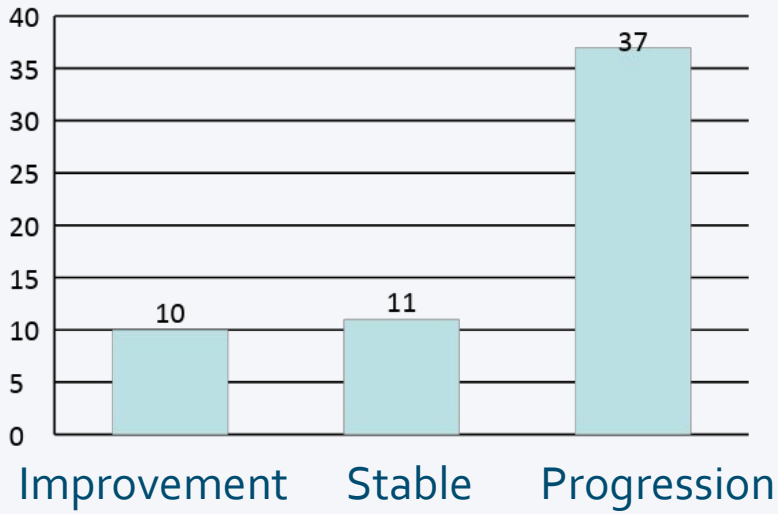
Image Interpretation is Variable



Before treatment

12 week Follow-up

Improvement?
Stable disease?
Progression?



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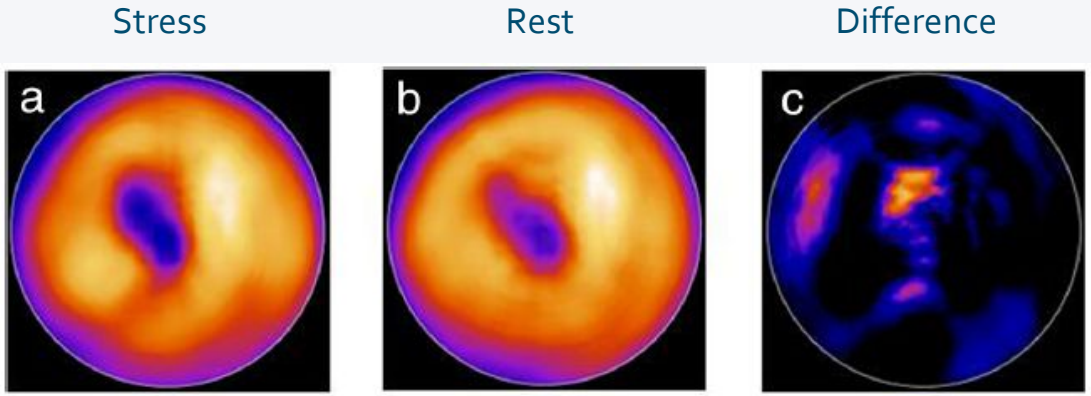
Delineation of Organs and Disease is Variable

Myocardial perfusion scintigraphy: *Delineate the area of ischemia*

11 physicians delineated area in 25 patients



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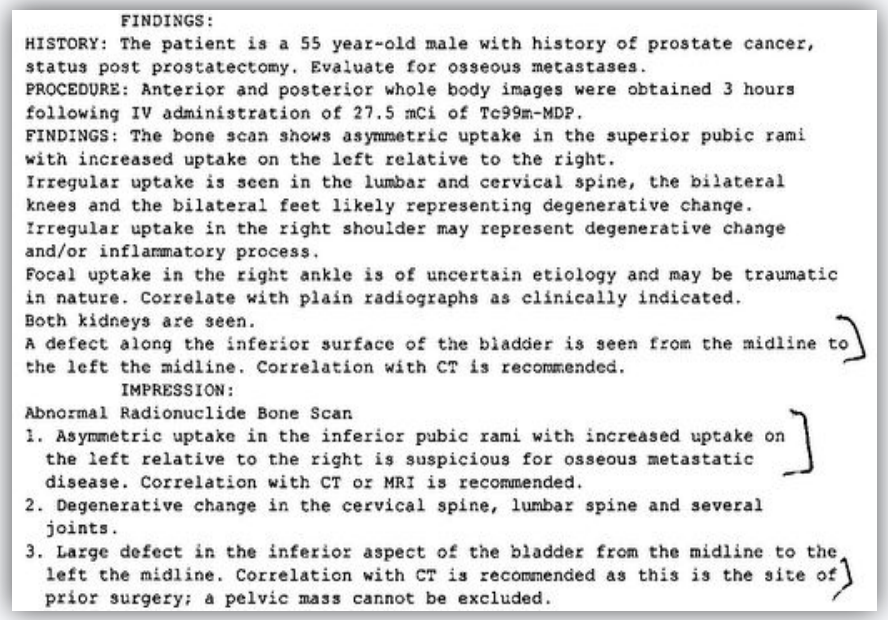
Variability Summary

- Assessments differ
  - Between physicians
  - Between centers
  - Between countries and cultures
  - Over time



FINDINGS:
HISTORY: The patient is a 55 year-old male with history of prostate cancer, status post prostatectomy. Evaluate for osseous metastases.
PROCEDURE: Anterior and posterior whole body images were obtained 3 hours following IV administration of 27.5 mCi of Tc99m-MDP.
FINDINGS: The bone scan shows asymmetric uptake in the superior pubic rami with increased uptake on the left relative to the right.
Irregular uptake is seen in the lumbar and cervical spine, the bilateral knees and the bilateral feet likely representing degenerative change.
Irregular uptake in the right shoulder may represent degenerative change and/or inflammatory process.
Focal uptake in the right ankle is of uncertain etiology and may be traumatic in nature. Correlate with plain radiographs as clinically indicated.
Both kidneys are seen.
A defect along the inferior surface of the bladder is seen from the midline to the left the midline. Correlation with CT is recommended.
IMPRESSION:
Abnormal Radionuclide Bone Scan
1. Asymmetric uptake in the inferior pubic rami with increased uptake on the left relative to the right is suspicious for osseous metastatic disease. Correlation with CT or MRI is recommended.
2. Degenerative change in the cervical spine, lumbar spine and several joints.
3. Large defect in the inferior aspect of the bladder from the midline to the left the midline. Correlation with CT is recommended as this is the site of prior surgery; a pelvic mass cannot be excluded.

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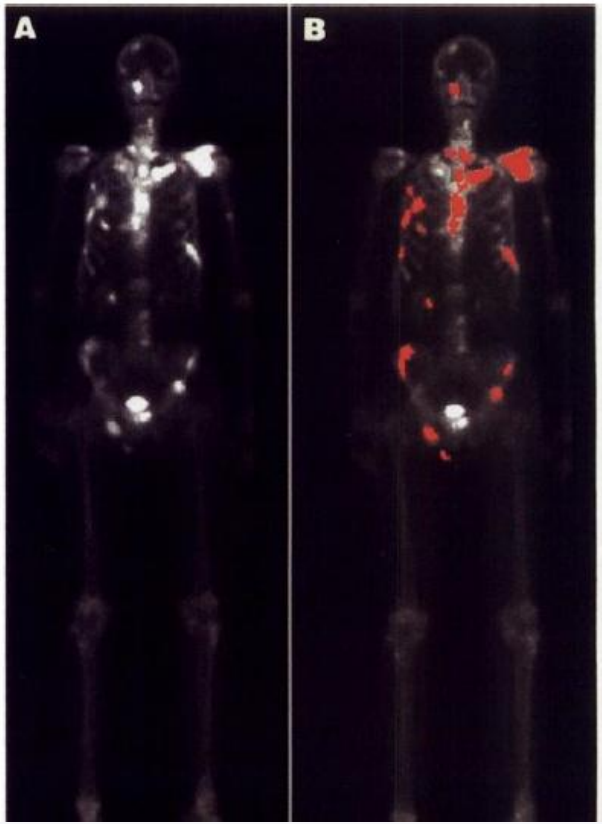
CAD Systems and Automated Imaging Biomarkers

- Automation (*where appropriate!*) is key
  - Objective
  - Repeatable
  - Reduces risk of oversight
  - Saves time
    - Mundane time consuming tasks completed in seconds
    - Better allocation of physician's time
  - Safe
    - Clear workflows and separation of concerns
      - E.g. technologists/nuclear medicine physicians
    - Quality is assured by unambiguous quality control workflows
  - Enables imaging assessments that are infeasible/impractical with manual tools

Bone Scan Index (BSI)

- **1997**: A manual method for quantification of whole-body bone scans was presented by a group at Memorial Sloan-Kettering Cancer Center, New York[1]
  - Bone Scan Index (BSI) reflects the skeletal involvement by tumor
- **1999**: BSI was associated with survival in patients with prostate cancer[2]
- **No widespread application**: The BSI method was manual, time-consuming, and not suitable for use in the clinical routine



[1]Erdi et al. J Nucl Med 1997; 38:1401

[2]Sabbatini et al. J Clin Oncol 1999;17:948

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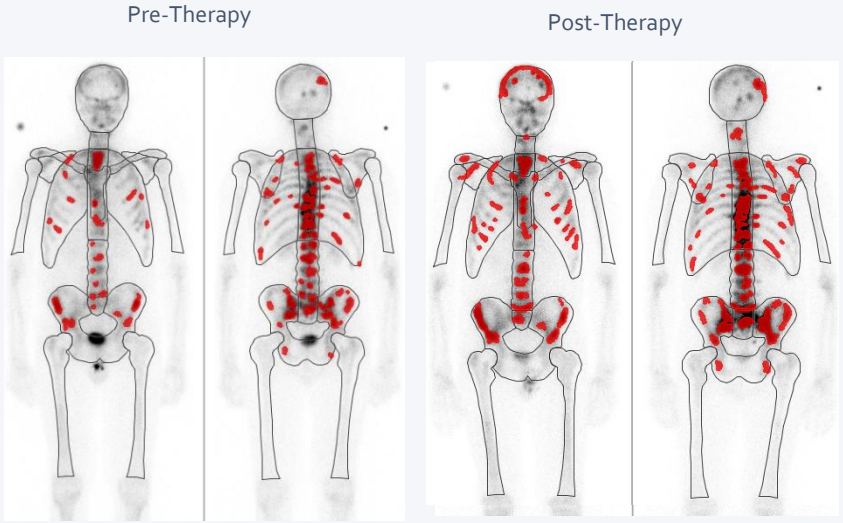
aBSI - Automated Bone Scan Index

- **2008**: Development of a stand-alone application
  - Used in over 1000 hospitals in Japan, Europe and the US
- Calculates BSI in seconds
- *Completely automated*
  - Corrections to classification of hotspots possible



	12/5/13	3/10/14
Bone Scan Index (%)	5.62	9.95
Number of high probability hotspots	59	73

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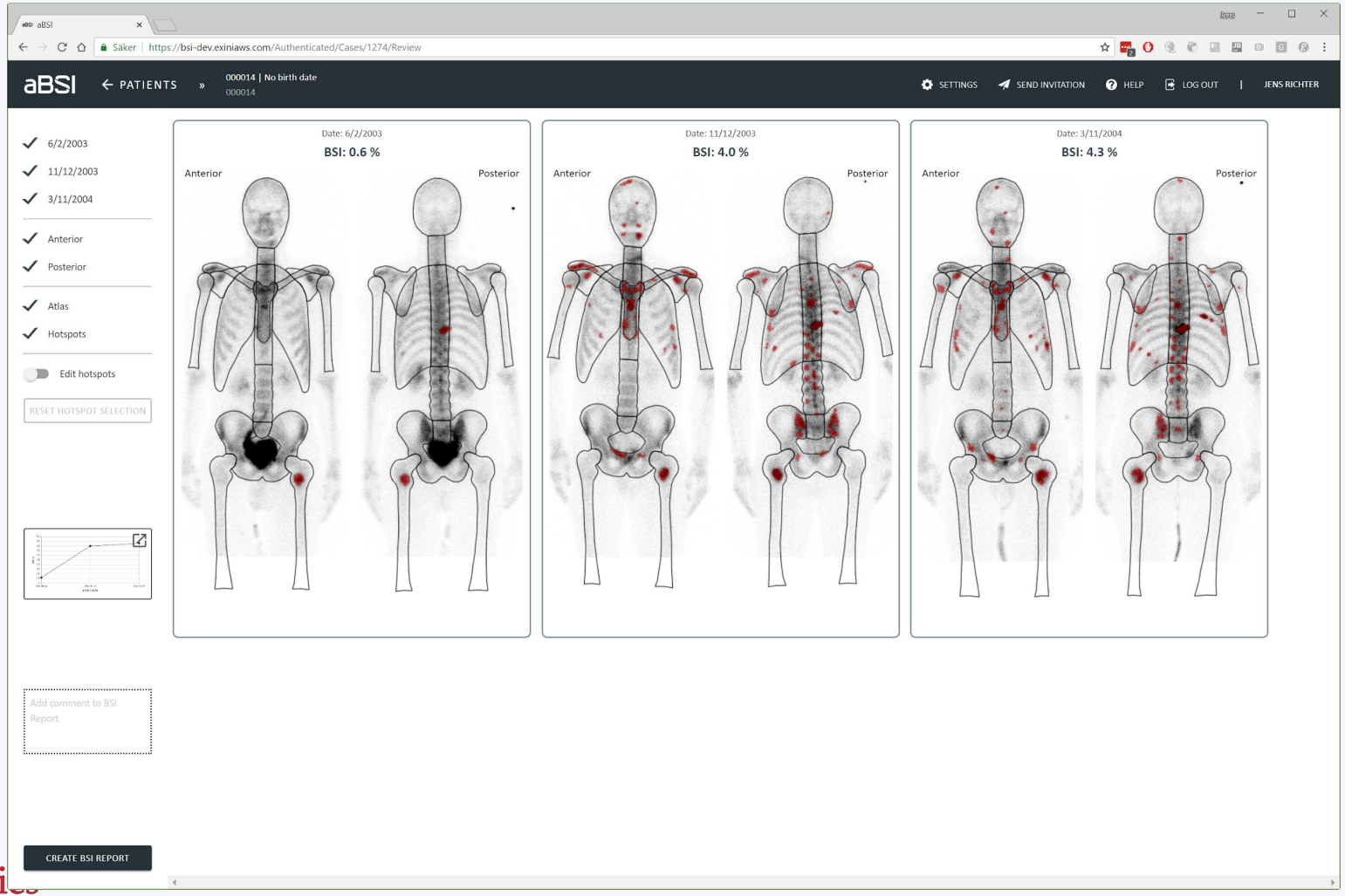

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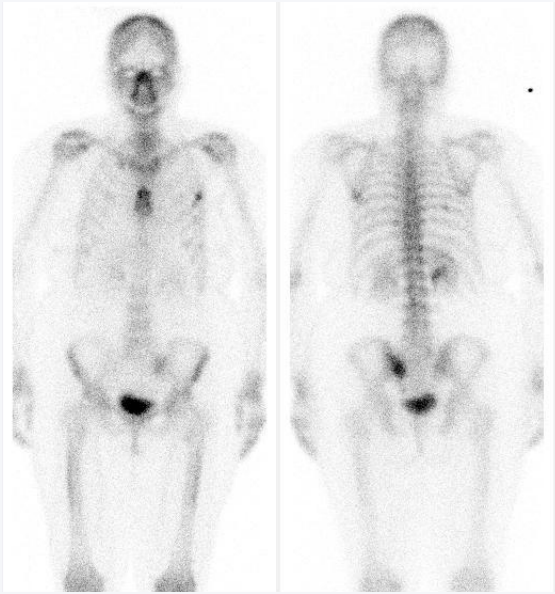
Do CAD Systems Work?

Metastatic Disease or not?
35 physicians interpreting 59 bone scans



18 of 35 physicians missed metastatic disease

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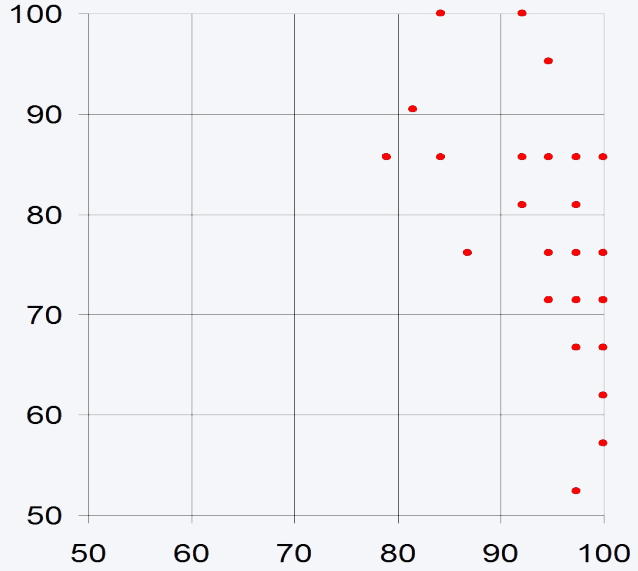
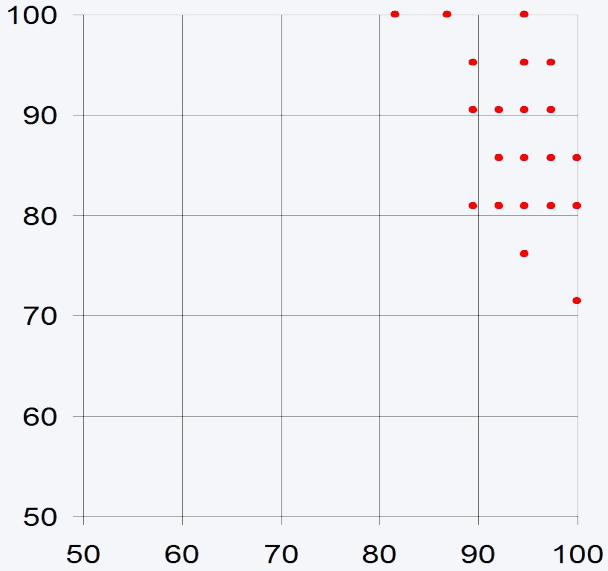
Do CAD Systems Work?

Sensitivity (%)



Sensitivity (%)



Sensitivity increased from 78% to 88%

$p<0.001$

Sadik et al. JNM 2008

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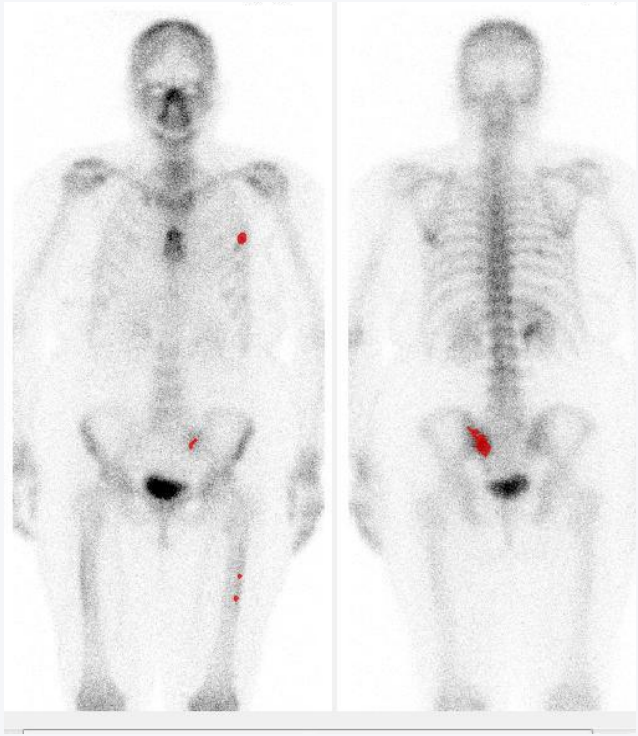
Do CAD Systems Work?



Number of physicians missing metastatic lesion:

- Without CAD 18/35
- With CAD 5/35

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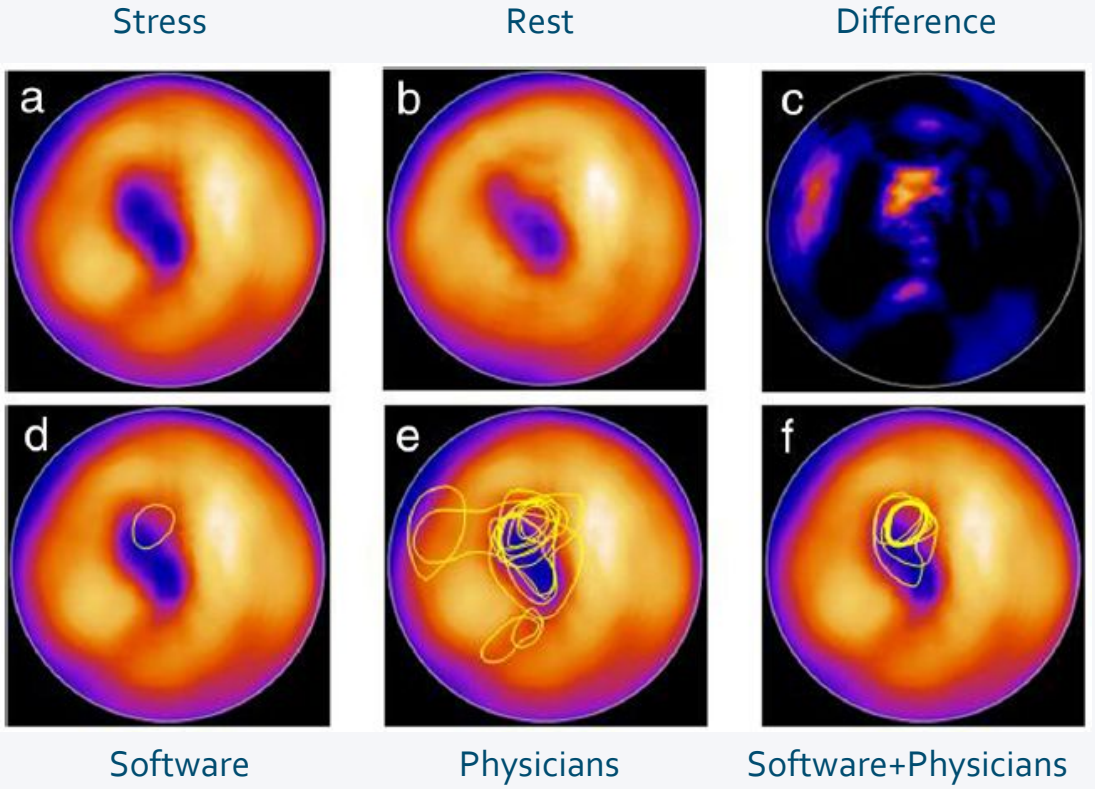
Sadik et al. J Nucl Med. 2009;50:368

Do CAD Systems Work?

Myocardial perfusion scintigraphy: *Delineate the area of ischemia*

11 physicians delineated area in 25 patients

- Before
- After suggestion from software



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aBSI - Validation

- An imaging biomarker must be proven in two ways
  - Analytical validation
    - Accuracy
    - Precision
    - Repeatability
  - Clinical validation
    - Predictive of clinical outcome
      - **Clinical use**: Approved/cleared by FDA - CDER
      - **Trial use**: Qualified by FDA - CDRH

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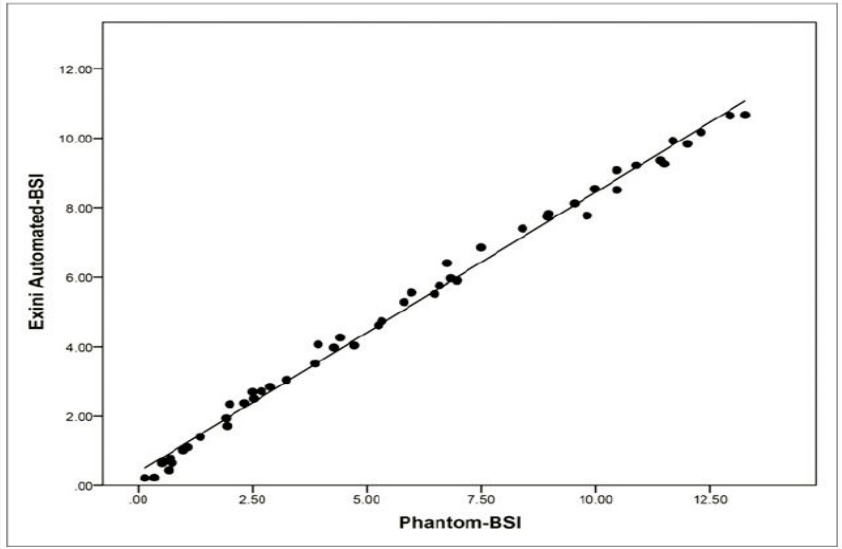
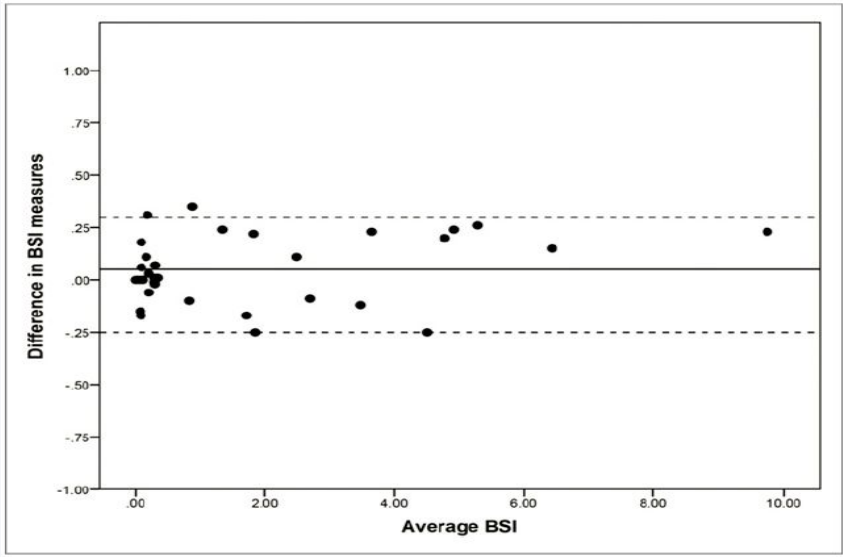
aBSI - Analytical Validation

JNM
The Journal of Nuclear Medicine

Analytic Validation of the Automated Bone Scan Index as an Imaging Biomarker to Standardize Quantitative Changes in Bone Scans of Patients with Metastatic Prostate Cancer

Aseem Anand[1,2], Michael J. Morris[2], Reza Kaboteh[3], Lena Båth[3], May Sadik[3], Peter Gjertsson[3], Milan Lomsky[3], Lars Edenbrandt[3,4], David Minarik[5] and Anders Bjartell[2,6]





Clinical Validation - Disease Stratification; Prognostic

JAMA Oncology | Original Investigation

Phase 3 Assessment of the Automated Bone Scan Index as a Prognostic Imaging Biomarker of Overall Survival in Men With Metastatic Castration-Resistant Prostate Cancer

A Secondary Analysis of a Randomized Clinical Trial

Andrew J. Armstrong, MD; Aseem Anand, PhD; Lars Edenbrandt, MD, PhD; Eva Bondesson, PhD; Anders Bjartell, MD, PhD; Anders Widmark, MD, PhD; Cora N. Sternberg, MD; Roberto Pili, MD; Helen Tuvesson, PhD; Örjan Nordle, PhD; Michael A. Carducci, MD; Michael J. Morris, MD

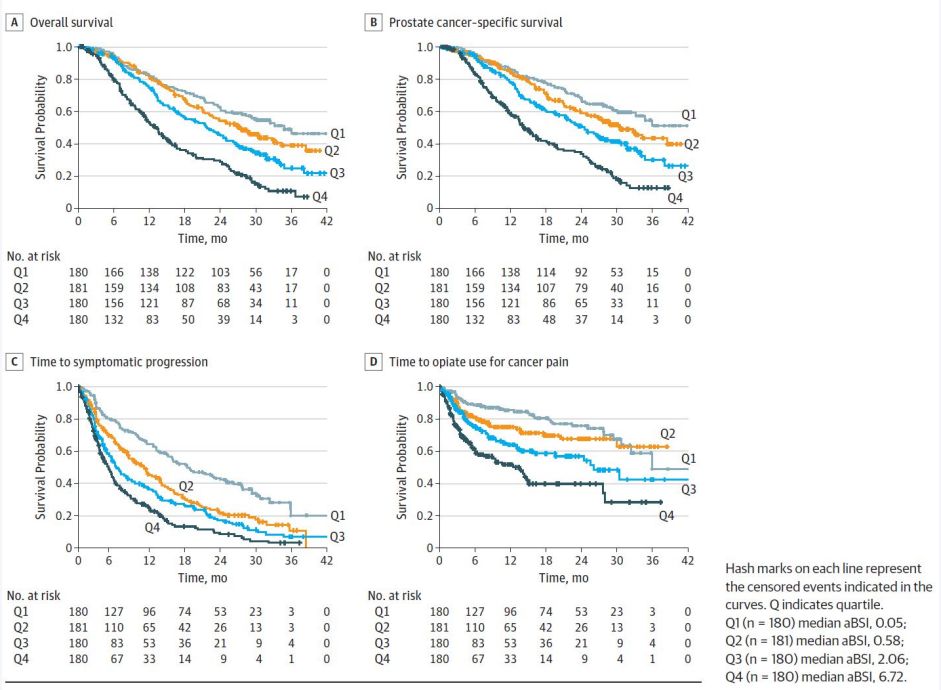
Table 1. Univariate and Bivariate Analyses Comparing the aBSI With the Number of Bone Lesions Among 709 Men

Analysis	Covariates	HR (95% CI)	*P* Value	C Index
Univariate	Lesion No.[a]	1.05 (1.03-1.06)	<.001	0.60
	aBSI[b]	1.15 (1.11-1.19)	<.001	0.63
Bivariate	Lesion No.[a]	1.02 (1.00-1.04)	.02	0.63
	aBSI[b]	1.12 (1.08-1.17)	<.001	

Abbreviations: aBSI, automated Bone Scan Index; HR, hazard ratio.

[a] Lesion numbers denoted with "greater than 20 or too many metastases to count" were assigned a value of 25.

[b] To accommodate the comparative analysis because of the lesion number threshold, aBSI values of 15 or higher were assigned a value of 15.



Hash marks on each line represent the censored events indicated in the curves. Q indicates quartile.
Q1 (n = 180) median aBSI, 0.05;
Q2 (n = 181) median aBSI, 0.58;
Q3 (n = 180) median aBSI, 2.06;
Q4 (n = 180) median aBSI, 6.72.

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3

Howard I. Scher, Michael J. Morris, Walter M. Stadler, Celestia Higano, Ethan Basch, Karim Fizazi, Emmanuel S. Antonarakis, Tomasz M. Beer, Michael A. Carducci, Kim N. Chi, Paul G. Corn, Johann S. de Bono, Robert Dreicer, Daniel J. George, Elisabeth I. Heath, Maha Hussain, Wm. Kevin Kelly, Glenn Liu, Christopher Logothetis, David Nanus, Mark N. Stein, Dana E. Rathkopf, Susan F. Slovin, Charles J. Ryan, Oliver Sartor, Eric J. Small, Matthew Raymond Smith, Cora N. Sternberg, Mary-Ellen Taplin, George Wilding, Peter S. Nelson, Lawrence H. Schwartz, Susan Halabi, Philip W. Kantoff, and Andrew J. Armstrong

Bone. The use of ^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesional number,[39] the bone scan index,[40,41] or lesion area,[42] is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form (Appendix Fig A3, online only). Areas/

Automated Characterization in PSMA Images

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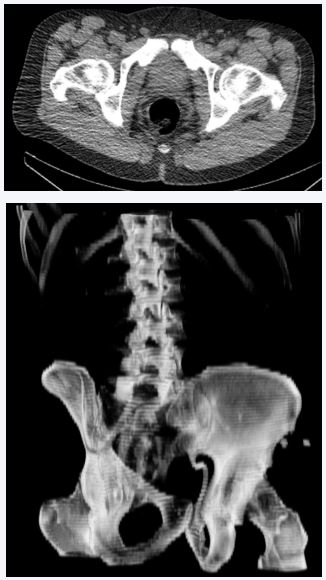
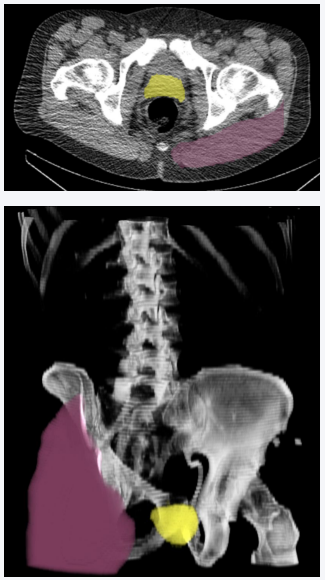
Automated Quantification of PSMA SPECT/CT

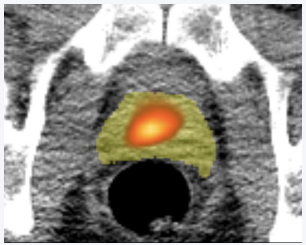
CT



CT + Segmentation



Segmentation + SPECT



Assessments

Prostate volume	
88.2	
Normal uptake average	
88.2	
Prostate uptake	
Max	1,312
Median	332
Mean	4.2
Total	5,205,153

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Methods

1. **Establish Deep Learning Algorithm**
   - Algorithm trained on 100 manually segmented diagnostic CTs
   - Algorithm includes Convolutional Neural Networks with 2.7M parameters
     - Designed to process both high- and low-dose CT images
     - Designed to process both full and part body scans
   - **Output:** max uptake within volumetric prostate segmentation

2. **Testing Algorithm in 1404 SPECT/CT images from clinical study**
   - Algorithm was evaluated using 68 1404 SPECT/CT images from a phase 2 study (1404-201)

3. **Manual assessment of 1404 SPECT/CT images**
   - The same images were evaluated manually per a standard read protocol in nuclear medicine
     - **Max uptake**: Manual placement of 2D ROI for max uptake measurement (Osirix MD)
     - **Segmentation**: Manual segmentation of prostate

4. **Comparison of automated and manual assessments**
   - The automated algorithm analytical performance was evaluated against results by manual read
     - **Max uptake**: Pearson correlation and slope of linear regression
     - **Segmentation**: Sorensen Dice Score (overlap)

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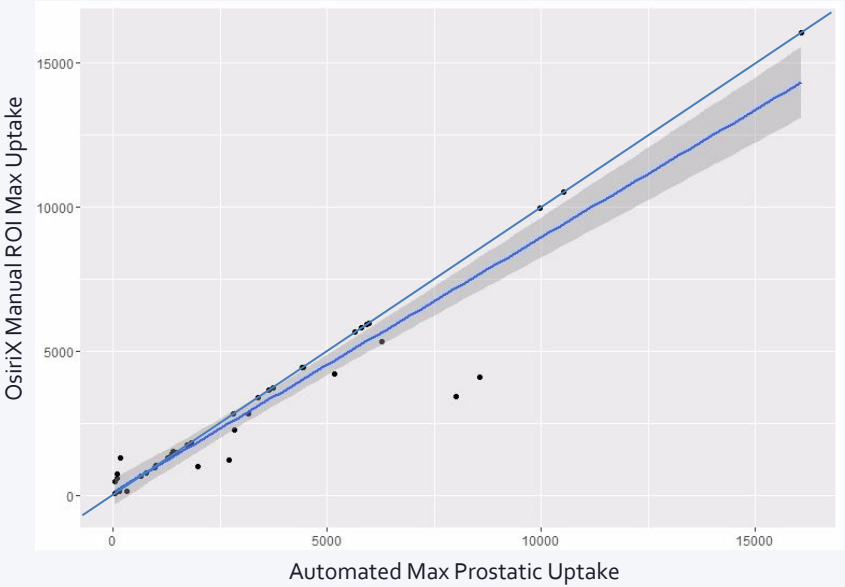
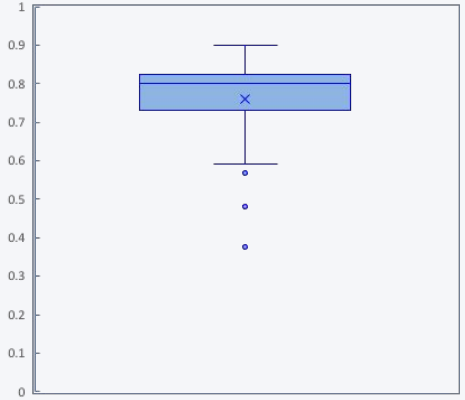
Results

Analysis of 1404 SPECT/CT images from clinical study (1404-201)





High correlation with manual reads

r = 0.95, p < 0.0001

Slope=0.89, 95%CI=[0.80,0.98]

Segmentation performance

- Prostate average DICE score **0.76**

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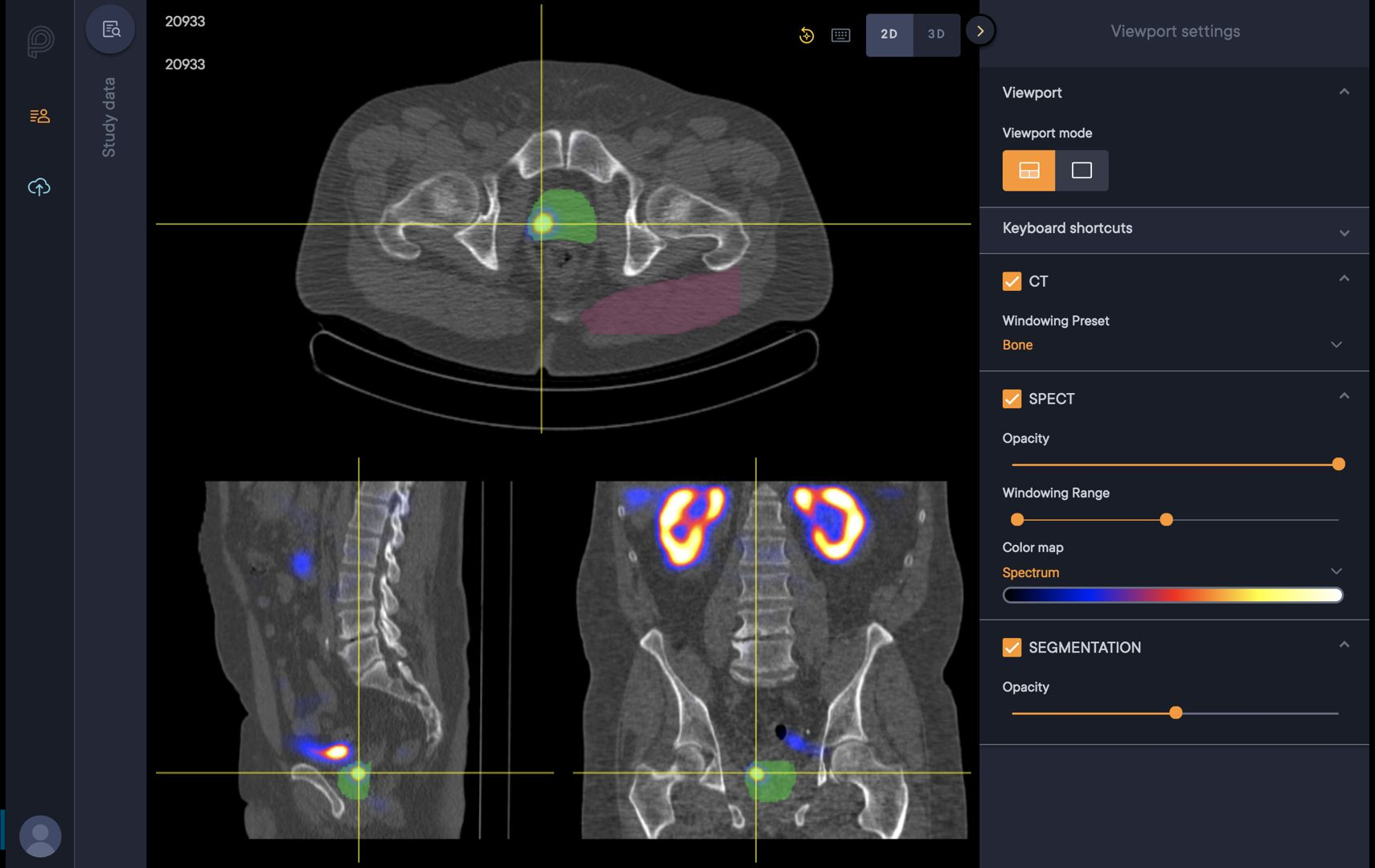
Study data
20933
20933
2D
3D
Viewport settings
Viewport
Viewport mode
Keyboard shortcuts
CT
Windowing Preset
Bone
SPECT
Opacity
Windowing Range
Color map
Spectrum
SEGMENTATION
Opacity

Summary

- Imaging biomarkers and related software works!
- aBSI thoroughly validated prognostic biomarker
- New imaging technologies (e.g. PSMA) and algorithms may transform prostate cancer diagnosis

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Thank You

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