Published in final edited form as:

Nucl Med Commun. 2012 April ; 33(4): 384–394. doi:10.1097/MNM.0b013e3283503ebf.

Computer-aided quantitative bone scan assessment of prostate cancer treatment response

Matthew S. Brown^a, Gregory H. Chu^a, Hyun J. Kim^a, Martin Allen-Auerbach^b, Cheryce Poon^b, Juliette Bridges^c, Adria Vidovic^c, Bharath Ramakrishna^a, Judy Ho^a, Michael J. Morris^d, Steven M. Larson^e, Howard I. Scher^d, and Jonathan G. Goldin^a

^aCenter for Computer Vision and Imaging Biomarkers, Department of Radiological Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles, California, USA

^bAhmanson Biological Imaging Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, California, USA

^cMedQIA, LLC, Los Angeles, California, USA

^dGenitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, New York, USA, and Department of Medicine, Weill Cornell Medical College, New York, New York

^eNuclear Medicine Service, Department of Medical Imaging, Memorial Sloan Kettering Cancer Center, New York, New York

Abstract

Objective—The development and evaluation of a computer-aided bone scan analysis technique to quantify changes in tumor burden and assess treatment effects in prostate cancer clinical trials.

Methods—We have developed and report on a commercial fully automated computer-aided detection system. Using this system, scan images were intensity normalized, then lesions identified and segmented by anatomic region-specific intensity thresholding. Detected lesions were compared against expert markings to assess the accuracy of the computer-aided detection system. The metrics *Bone Scan Lesion Area*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Count* were calculated from identified lesions, and their utility in assessing treatment effects was evaluated by analyzing before and after scans from metastatic castration-resistant prostate cancer patients: 10 treated and 10 untreated. In this study, patients were treated with cabozantinib, a MET/VEGF inhibitor resulting in high rates of resolution of bone scan abnormalities.

Correspondence to Dr. Matthew S. Brown, PhD, UCLA Department of Radiological Sciences, 924 Westwood Blvd, Suite 615, Los Angeles, California, 90024 USA.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial disclosure: Matthew S. Brown and Jonathon G. Goldin are directors of MedQIA. Juliette Bridges and Adria Vidovic are employees of MedQIA. Howard I. Scher receives institutional research support and acts as a consultant (uncompensated) for Exelixis, Inc. Gregory Chu, Hyun J. Kim, Martin Allen-Auerbach, Cheryce Poon, Bharath Ramakrishna, Judy Ho, Michael J. Morris, and Steven M. Larson have no conflicts of interest to declare.

Data was presented previously at ASCO 2011 and published as abstract in *J Clin Oncol* 29: 2011 (suppl; abstr e15169)

MSB, GHC, HJK, MJM, SML, HIS, JGG designed the experiments. JB, JH acquired data. GHC, MAA, CP, AV, BR analyzed the data. HJK performed statistical analysis. MSB, GHC, HJK, HIS, JGG reviewed and interpreted statistical analysis. All authors contributed to drafting and revising the article, and gave their final approval for publication

Results—Our automated computer-aided detection system identified bone lesion pixels with 94% sensitivity, 89% specificity, and 89% accuracy. Significant differences in changes from baseline were found between treated and untreated groups in all assessed measurements derived by our system. The most significant measure, *Bone Scan Lesion Area*, showed a median (interquartile range) change from baseline at week 6 of 7.13% (27.61) in the untreated group compared with −73.76% (45.38) in the cabozantinib-treated group ($P = 0.0003$).

Conclusions—Our system accurately and objectively identified and quantified metastases in bone scans, allowing for interpatient and inpatient comparison. It demonstrates potential as an objective measurement of treatment effects, laying the foundation for validation against other clinically relevant outcome measures.

Keywords

computer-assisted detection; bone neoplasms; computer-assisted image processing; bone scan; radionuclide imaging; prostate cancer

Introduction

More than 90% of patients with advanced prostate cancer develop bone metastases [1], which can produce some of the most severe complications of the disease, including pain and spinal cord compromise. In addition to quality-of-life concerns, more extensive bone disease is associated with shorter survival times in these patients [2–6].

Whole-body bone scintigraphy is a highly sensitive method for visualizing bone metastases and is the accepted standard imaging modality for detection of metastases and assessment of treatment outcomes. But, despite decades of use, there remains no established standard for evaluating and interpreting the imaging results. As a result, most reports are subjective and often do not accurately reflect disease status. Recent studies have indicated that false-negatives occur at an unacceptably high rate, with nontrivial differences in interphysician and intraphysician interpretation [7,8]. Pseudoprogression of disease, wherein an apparent worsening on scan may in fact represent clinical benefit [9], is particularly problematic and may lead to the premature discontinuation of a drug to which a patient is responding. Response Evaluation Criteria in Solid Tumors (RECIST), the standard guideline used to assess outcomes in solid tumor malignancies, also falls short in evaluating treatment effects in prostate cancer, as bone lesions are “nonmeasurable” with RECIST [10].

Having noted that there were no validated criteria for response assessment on bone scan and no therapies that consistently produced scan improvement, the Prostate Cancer Working Group 2 (PCWG2) focused their recommendations on disease progression. They proposed to study the clinical significance of the development of new lesions on scan as an outcome measure for clinical trials. It is noteworthy that the detection of new lesions on a first scan required the documentation of additional new lesions on a subsequent scan for a patient to be considered as having progressed. Clinical qualification of this outcome is ongoing in phase III trials. PCWG2 did not address the significance of changes in intensity, size, or area of individual lesions, all of which are limited by the challenges of subjective, visual lesion detection [11]. The simple conventional metric of lesion counting is of limited value when assessing treatment effects, as lesions may decrease in size without changing in number or may break into smaller components and, thus, superficially appear as increased metastatic burden. There is an urgent need for an objective, consistent, and reproducible approach to lesion detection and quantitative assessment of disease burden before bone scans can play an effective role in treatment outcome assessment.

A small number of computer-aided lesion detection systems have been reported for bone scans. These techniques have included semiautomated image segmentation programs that are frequently too time-consuming for use in a clinical setting [12,13]. The semiautomated approach described by Erdi et al [12] requires that the user insert a seed point in each metastatic region on the image, a process that is nontrivial, considering that patients with bone metastases often have multiple disease sites. More recently, a fully automated method developed by Sadik et al [14] combines bone lesion detection by image segmentation with scan evaluation via an artificial neural network to classify patients by their probability of bone metastasis, resulting in a binary grading of scans as having probable “bone metastases” or probable “no bone metastases.” While this system showed good correlation with physician-determined estimates of the probability of bone metastases, the system does not provide a quantitative metric for the comparison of consecutive scans nor a means of assessing treatment outcomes. Importantly, none of the reported outcomes have been studied prospectively in relation to true measures of patient benefit such as reduction in skeletal-related events or prolongation of life, measures that form the basis for regulatory approvals. Conversely, systems for image enhancement have been developed to normalize images from consecutive scans for ease of physician interpretation [15] but have not attempted lesion identification.

Quantitative assessment by bone scintigraphy of metastatic bone disease burden in prostate cancer has been previously performed, including the development of metrics such as bone scan index (BSI) and percentage of the positive area on a bone scan (%PABS) [16,17]. Both BSI and %PABS have undergone initial evaluation as prognostic factors for prostate cancer patients, but the methods used to calculate these metrics have been time-consuming, requiring extensive manual annotation of bone scans. Evaluation of %PABS [18] and BSI [19] as feasible metrics for the assessment of treatment response is ongoing.

The effective use of bone scans to monitor treatment effects requires the accurate segmentation and quantification of lesions within a single scan, as well as the comparison of lesion measurements between consecutive scans. Computer-aided detection (CAD) systems have been previously applied to bone scan analysis but have typically addressed lesion detection only on a scan-by-scan basis, without provisions for comparing successive scans. The purpose of our study was to develop an automated system that accurately and reproducibly segments and quantifies bone lesions to aid physicians in inpatient and outpatient comparison.

Here we present the analytical validation of a bone scan computer-aided treatment assessment (CADrx) system that combines both automated lesion segmentation, including image normalization, and quantitative assessment of disease burden. To evaluate the utility of our CAD system in this capacity, we examined before and after scans from untreated and cabozantinib-treated metastatic castration-resistant prostate cancer (CRPC) patients. In this study, patients were treated with cabozantinib, a small-molecule inhibitor of the receptor tyrosine kinases MET and vascular endothelial growth factor receptor 2 [20]. In ongoing phase II trials, treatment with cabozantinib has shown promising antitumor activity in a number of tumor types, including metastatic CRPC, in which its use has resulted in a high rate of complete or partial resolution of bone scan abnormalities [21,22]. Successful differentiation between untreated and cabozantinib-treated patient groups may therefore be a useful means of evaluating the potential of a CAD system in assessing treatment effects, although the system could be applied to evaluate any treatment producing bone scan changes.

Our objective in developing this CADrx system was to reduce the variability of hand-annotated bone scan analysis, so that objective, reproducible, and quantitative measurements

could be obtained consistently, thereby laying the foundation for prospective correlation of individual measures with other clinical and laboratory outcome data. The goals of this work were to (a) develop and test the accuracy of automated bone scan lesion segmentation (detection of lesion pixels) and (b) derive quantitative measures of lesion burden that may then be used to assess disease status changes in treated and untreated CRPC patient groups.

Materials and Methods

Image data sets

Three data sets were used in the development and evaluation of the CADrx system. Two reference sets were used for developing the lesion segmentation technique, specifically to determine intensity normalization and lesion thresholding parameters. A separate test set was used to evaluate the CADrx system. Scans from all three data sets were obtained from an anonymized research database of CRPC patients who underwent standard of care whole body scintigraphy. Bone scans were obtained 2 to 4 hours post injection of between 740 and 925 MBq of ^{99m}Tc -methylene diphosphonate. Anterior and posterior whole-body images were recorded digitally. Image data were acquired at multiple centers (18 total) using different gamma cameras (9 different scanner models), with pixel size ranging from 2.06 – 2.40 mm.

Lesion segmentation threshold reference set—A total of 44 bone scans of subjects with metastatic CRPC from our research database were reviewed by an experienced, board-certified nuclear medicine physician. Two cases were excluded for having no metastatic bone lesions, two were of poor image quality, and one was excluded because of incorrect pixel spacing in the DICOM header. The remaining reference set of 39 scans was used in the development phase to determine intensity thresholds for lesion detection. The reference set included scans that varied in quality, intensity distributions, and contrast without restriction.

Intensity normalization reference set—From the reference set, the nuclear medicine physician selected a subset of 20 representative scans of superior quality, with consideration for intensity distribution, image contrast, patient positioning, and image acquisition. These scans were used to determine intensity normalization parameters.

Test set—To evaluate the CADrx system, an independent test set of scans was used, comprising scans from 20 metastatic CRPC patients who had failed at least two prior lines of drug therapy. After their baseline scan, 10 patients received cabozantinib treatment (100 mg daily; Exelixis, Inc, South San Francisco, CA), while 10 patients received no treatment. A second scan acquired 6 to 24 weeks after the baseline scan was then also analyzed by the CADrx system. All aspects of imaging were standardized, and images were reviewed for acceptable quality.

CAD system development

A CADrx system for bone scan assessment was developed within the Imaging Biomarker Information System (IBIS) for image markup and analysis (MedQIA, LLC, Los Angeles, CA). The IBIS markup system combines image review capabilities with computer-aided tools for region segmentation, quantitative analysis, and data export for clinical trials. In the CADrx system, anterior and posterior bone scan images are processed with pixel intensity normalization and lesion segmentation, followed by quantitative assessment of lesion burden.

Atlas-based anatomic segmentation—To enable lesion pixel detection from anatomy-specific thresholding, the image is first segmented into anatomic regions by registering to an

atlas image with the following anatomic labels: sternum, spine, ribs, head, extremities, and pelvis (Fig. 1). Image registration is performed in two steps. First, a rigid registration is applied to obtain a global alignment of the two images, as implemented in Mattes et al [23]. Mattes mutual information metric is used as the cost function, which is optimized via a regular step gradient descent algorithm. Subsequently, a nonrigid registration is performed to account for local differences between the atlas and subject images, using a mean squares metric and based on the four-step demons algorithm presented in Calchier et al [24]. The Insight Segmentation and Registration Toolkit [25] is used for implementation of the registration process.

Intensity normalization—Bone scans may vary greatly in intensity because of differences in body habitus, radiotracer dosing levels, and/or time between tracer administration, scanner type, and scan acquisition parameters (Fig. 2A). To improve reproducibility of lesion segmentation and quantitation, the CADrx system first normalizes the intensities of the test bone scans using a reference set of representative bone scans.

Following atlas-based segmentation of the extremities region, the pixel intensities of a test bone scan image are normalized by extraction of the 75th centile from the intensity histogram to represent the intensity of normal bone. This centile was also derived for each image in the intensity normalization reference set of 20 high-quality bone scans. The ratio of normal bone intensity from the test image to the median normal bone intensity in the reference set is used to linearly rescale all pixels in the test image. The resultant rescaled, or normalized, patient image therefore has a normal bone intensity matching that of the reference set. After normalization, the pixel intensities of normal bone are consistent between time points, allowing for reproducible lesion segmentation and quantitative assessment (Fig. 2B) in serial patient images.

Lesion segmentation via anatomic region-specific intensity thresholding—To identify an intensity threshold for lesion segmentation in each anatomic region, the reference set of 39 bone scans from patients with metastatic CRPC was used. Lesions in the reference set were manually annotated by an experienced nuclear medicine physician. These expert markings were classified as true-positive pixels and other bone pixels as true-negatives. At a given threshold, sensitivity and specificity were calculated for each anatomic region (rib and head, sternum, spine, pelvis, or extremities) for each patient, and subsequently used to calculate mean sensitivity and mean specificity across patients. Since there could be multiple or no lesions present in a given anatomic region of a single patient, mean sensitivity and specificity were calculated per region in each patient. Mean receiver operating characteristic (ROC) was graphed, where the mean sensitivity and mean false-positive rate (i.e. $1 - \text{specificity}$) were derived by varying the intensity threshold in the anatomic region (Fig. 2C). Intensity thresholds were chosen that maximized the number of true-positives (increased sensitivity) while minimizing the number of false-positives (increased specificity).

When processing a test image, intensity normalization is first performed, then lesions that are consistent with metastatic foci of disease are automatically segmented based on anatomic region-specific intensity thresholds previously determined by ROC analysis for the head, sternum, spine, pelvis, ribs, and extremities. An example of the results of lesion segmentation is given in Fig. 3A. Lesions are identified as regions of greater than five contiguous pixels with intensities above the anatomic region-specific threshold level, thereby removing random speckle noise. Each segmented image is then reviewed by a nuclear medicine physician for removal of any remaining false-positive regions (e.g., areas of degenerative joint disease).

Quantitative assessment of lesion burden—Three quantitative measures of overall lesion burden were investigated. Total *Bone Scan Lesion Area* is summed as

$Bone\ Scan\ Lesion\ Area = \sum_{p \in R} A_p$, where R is the set of pixels identified as bone lesion, and A_p is the area of pixel p (in cm^2). The mean normalized *Bone Scan Lesion Intensity* is computed by averaging the normalized intensity values of the pixels identified as comprising a lesion. Mean normalized *Bone Scan Lesion Intensity* is computed as

$Bone\ Scan\ Lesion\ Intensity = \sum_{p \in R} I_p / N_R$, where R is the set of pixels identified as bone lesion, I_p is the intensity of pixel p , and N_R is the number of pixels in R . The *Bone Scan Lesion Area* measure thus represents a quantification of the size and number of active regions on the bone scan, while the *Bone Scan Lesion Intensity* represents the level of bone formation activity. *Bone Scan Lesion Count* was also assessed as the number of discrete regions of at least five contiguous pixels over the determined intensity threshold.

In Fig. 3B, changes from baseline in *Bone Scan Lesion Area*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Count* between the two indicated time points are shown for the depicted patient. On the follow-up scan the bone lesions have reduced in size but have not changed in number. These changes are reflected by the reductions in *Bone Scan Lesion Area* and *Bone Scan Lesion Intensity*, while the conventional measurement of *Bone Scan Lesion Count* remains unchanged. This example illustrates the potential increased sensitivity of CADrx analysis over conventional lesion counting.

Analytical validation

Lesion segmentation accuracy assessment—The CADrx system was initially run on the test set without any user editing of the results. The fully automated segmentation results were evaluated against manual tumor contouring by a research associate experienced in bone scan analysis; this evaluation was reviewed and edited by a nuclear medicine physician without access to the CADrx system. Accuracy was assessed, using the expert markings, as true-positive pixels and as true-negative pixels.

Evaluation of lesion burden measures for assessment of treatment effects—After testing its accuracy against manual expert lesion markings, we evaluated the CADrx system as a means of monitoring treatment effects. The CADrx system was run on the test dataset of bone scans (treated and untreated subjects), and areas of uptake consistent with nonmalignant disease (e.g. degenerative joint) were manually removed by a board-certified nuclear medicine physician. *Bone Scan Lesion Count*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Area* were calculated for visit 1 and visit 2 scans. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to test for differences between treated and untreated groups in the ratio of *Bone Scan Lesion Count* (visit 2/visit 1), percent change in *Bone Scan Lesion Intensity* from baseline, and percent change in *Bone Scan Lesion Area* from baseline.

Results

Lesion segmentation accuracy assessment

In fully automated mode, the CADrx system showed a median (interquartile range) sensitivity of 94.1% (8.8), specificity of 89.2% (9.3), and accuracy of 89.4% (8.3) for tumor pixels on bone scans as compared with visual assessment by experienced nuclear medicine physicians. These results demonstrate that our CADrx system can automatically detect lesion pixels on bone scans with high accuracy, providing a platform for reproducible quantitative assessment of lesion burden.

Evaluation of lesion burden measures for assessment of treatment effects

To evaluate the utility of our CADrx system in monitoring treatment effects, we evaluated before and after scans from untreated and cabozantinib-treated metastatic CRPC patients. Baseline and successive scans from two representative cabozantinib-treated patients along with the results from CADrx analysis are shown (Figs. 4 and 5). In both patients, quantification of *Bone Scan Lesion Count*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Area* demonstrate substantial reductions by week 6, following treatment with cabozantinib. In one of the representative patients (see Fig. 5), all measurements equal zero by week 6, indicating complete bone scan resolution. Baseline *Bone Scan Lesion Count*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Area* were not statistically different ($P = 0.52, 0.87$, and 0.82 , respectively) between the cabozantinib-treated and untreated groups (Table 1). Following treatment with cabozantinib, the differences between the two groups were significantly different for each measure ($P = 0.0012, 0.0019$, and 0.0003 , respectively) (Table 2 and box plots in Fig. 6), demonstrating that these objective, quantitative measurements may be used to assess and compare treatment effects as visualized on bone scans.

Discussion

The automated CADrx system accurately and reproducibly detected, segmented, and quantified individual bone lesions from whole body scintigraphy scans, enabling the quantitative assessment of tumor burden at baseline and following treatment. Key to this functionality was the use of ROC analysis as a rigorous, statistical method for the selection of anatomic region-specific intensity thresholds. These intensity thresholds give consistent inpatient and outpatient lesion detection and measurement, resulting in low measurement variability and allowing for differentiation between treatment groups. We have analytically validated three new imaging biomarkers computed using this system, *Bone Scan Lesion Area*, *Bone Scan Lesion Intensity*, and *Bone Scan Lesion Count*, and demonstrated significant differences in each of these parameters following treatment with cabozantinib. Prospective trials to qualify these biomarkers are ongoing.

This CADrx system was developed to enable the reliable detection and quantification of disease burden, minimizing the variability inherent in manual assessment of bone scan images, thereby allowing for objective and reproducible assessment of change over time. In our evaluation of the lesion segmentation accuracy of our CADrx system against expert manual lesion markings, we found that false-positives were primarily due to areas of uptake consistent with degenerative joint disease, which the radiotracer imaging agent highlights in addition to sites of metastatic disease. These false-positives were effectively removed during physician review, the only stage of analysis in this study requiring intervention by the clinician. Physicians focus on removal of tracer uptake due to degenerative changes in the joints rather than in regions such as the lumbar spine (areas where both metastases and degenerative changes are frequent). In addition, further algorithm development may allow for the automatic identification and removal of false-positives consistent with sites of nonmalignant (e.g. degenerative joint) disease.

Even including false-positives from nonmalignant disease, our CADrx system compared favorably in terms of accuracy to currently available CAD systems of bone scan assessment. Manual interpretation of bone scans is reported to have on average ~77% sensitivity and 84% to 96% specificity, when compared against gold standard assessment by one or several experienced clinicians [8,26]. Sadik et al [8] reported that their CAD system had 90% sensitivity and 89% specificity in classifying patients by the probable presence or absence of metastases, when compared against the final clinical assessment of each case. In comparison, our CADrx system demonstrated better sensitivity and comparable specificity

(94% and 89%, respectively). In addition, unlike CAD systems currently available, our system provides automated quantification of the bone lesions, allowing for objective comparisons between scans and treatment groups, which may then be useful for monitoring of treatment effects.

Our assessment of the CADrx system in evaluating changes in disease burden over time suggests that these quantitative measurements can successfully differentiate between cabozantinib-treated and untreated patient groups. Of the three measures investigated, *Bone Scan Lesion Area* showed the greatest differentiation between treatment groups, as reflected by the box plots and statistical *P* value. The data indicate that total *Bone Scan Lesion Area* may be a useful indicator for early-treatment response in metastatic CRPC patients. Patients in the untreated group demonstrated a percent change from baseline in *Bone Scan Lesion Area* that ranged from -23.3% to 315.0%. Therefore, based on the lower bound, a conservative 30% reduction in *Bone Scan Lesion Area* from baseline is appropriate as a cutoff point to distinguish responders from nonresponders. This result has potential utility for monitoring effects of treatment and will be explored further in future studies.

Conclusion

Our automated CADrx system accurately and objectively identifies metastases on the bone scans of CRPC patients, allowing for reproducible quantification of lesion burden and subsequent interpatient and inpatient comparison. The CADrx measurements have potential for objective assessment of treatment effects visualized on bone scans based on separation of treated and untreated patient groups. These initial studies lay the foundation for validating these measurements in CRPC and other tumor types against other clinically relevant outcome measures, such as pain relief and overall survival in larger randomized cohorts.

Acknowledgments

We would like to thank Cheryl Chun (BlueMomentum) for medical writing assistance. Funding for medical writing support was provided by Exelixis, Inc.

Financial support: Funding for medical writing support was provided by Exelixis, Inc. Howard I. Scher was supported in part by NCI SPORE in Prostate Cancer (P50 CA92629) and the Department of Defense/Prostate Cancer Foundation-Prostate Cancer Clinical Trials Consortium (PC071610). Steven M. Larson was supported in part by the NIH, the Starr Foundation, and the Ludwig Institute for Cancer Research.

References

1. Carlin BI, Andriole GL. The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*. 2000; 88(12 Suppl):2989–2994. [PubMed: 10898342]
2. Sonpavde G, Pond GR, Berry WR, de Wit R, Eisenberger MA, Tannock IF, et al. The association between radiographic response and overall survival in men with metastatic castration-resistant prostate cancer receiving chemotherapy. *Cancer*.
3. Logothetis CJ, Navone NM, Lin SH. Understanding the biology of bone metastases: key to the effective treatment of prostate cancer. *Clin Cancer Res*. 2008; 14:1599–1602. [PubMed: 18347159]
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001; 27:165–176. [PubMed: 11417967]
5. Coleman R, Heidenreich A, Bell R. Managing metastatic bone disease: three case studies. *Semin Oncol*. 2004; 31(5 Suppl 10):83–86. [PubMed: 15490382]
6. Sabbatini P, Larson SM, Kremer A, Zhang ZF, Sun M, Yeung H, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol*. 1999; 17:948–957. [PubMed: 10071289]

7. Peters AM, Bomanji J, Costa DC, Ell PJ, Gordon I, Henderson BL, et al. Clinical audit in nuclear medicine. *Nucl Med Commun*. 2004; 25:97–103. [PubMed: 15154696]
8. Sadik M, Suurkula M, Höglund P, Järund A, Edenbrandt L. Quality of planar whole-body bone scan interpretations—nationwide survey. *Eur J Nucl Med Mol Imaging*. 2008; 35:1464–1472. [PubMed: 18373092]
9. Ryan CJ, Shah S, Efstathiou E, Smith MR, Taplin ME, Bubley GJ, et al. Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res*. 2011; 17:4854–4861. [PubMed: 21632851]
10. Scher HI, Morris MJ, Kelly WK, Schwartz LH, Heller G. Prostate cancer clinical trial end points: "RECIST"ing a step backwards. *Clin Cancer Res*. 2005; 11:5223–5232. [PubMed: 16033840]
11. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol*. 2008; 26:1148–1159. [PubMed: 18309951]
12. Erdi YE, Humm JL, Imbriaco, Yeung H, Larson SM. Quantitative bone metastases analysis based on image segmentation. *J Nucl Med*. 1997; 38:1401–1406. [PubMed: 9293797]
13. Yin TK, Chiu NT. A computer-aided diagnosis for locating abnormalities in bone scintigraphy by a fuzzy system with a three-step minimization approach. *IEEE Trans Med Imaging*. 2004; 23:639–654. [PubMed: 15147016]
14. Sadik M, Jakobsson D, Olofsson F, Ohlsson M, Suurkula M, Edenbrandt L. A new computer-based decision-support system for the interpretation of bone scans. *Nucl Med Commun*. 2006; 27:417–423. [PubMed: 16609352]
15. Jeong CB, Kim KG, Kim TS, Kim SK. Comparison of image enhancement methods for the effective diagnosis in successive whole-body bone scans. *J Digit Imaging*. 2011; 24:424–436. [PubMed: 20195695]
16. Imbriaco M, Larson SM, Yeung HW, Mawlawi OR, Erdi Y, Venkatraman ES, et al. A new parameter for measuring metastatic bone involvement by prostate cancer: the Bone Scan Index. *Clin Cancer Res*. 1998; 4:1765–1772. [PubMed: 9676853]
17. Noguchi M, Kikuchi H, Ishibashi M, Noda S. Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. *Br J Cancer*. 2003; 88:195–201. [PubMed: 12610502]
18. Yahara J, Noguchi M, Noda S. Quantitative evaluation of bone metastases in patients with advanced prostate cancer during systemic treatment. *BJU Int*. 2003; 92:379–384. [PubMed: 12930424]
19. Morris, MJ.; Jia, X.; Larson, SM.; Kelly, A.; Mezheritzky, I.; Stephenson, RD.; Heller, G.; Scher, HI. Post-treatment serial bone scan index (BSI) as an outcome measure predicting survival. Presented at: Genitourinary Cancers Symposium; February 14–16, 2008; Alexandria, VA. 2008. Abstract 189.
20. You WK, Sennino B, Williamson CW, Falcón B, Hashizume H, Yao LC, et al. VEGF and c-Met blockade amplify angiogenesis inhibition in pancreatic islet cancer. *Cancer Res*. 2011; 71:4758–4768. [PubMed: 21613405]
21. Gordon MS, Vogelzang NJ, Schoffski P, Daud A, Spira AI, O'Keeffe BA, Rafferty T, Lee Y, Berger R, Shapiro G. Activity of cabozantinib (XL184) in soft tissue and bone: Results of a phase II randomized discontinuation trial (RDT) in patients (pts) with advanced solid tumors. *J Clin Oncol*. 2011; 29 (suppl; abstr 3010).
22. Hussain M, Smith MR, Sweeney C, Corn PG, Elfiky AA, Gordon MS, Haas NB, Harzstark AL, Kurzrock R, Lara P Jr, Lin CC, Sella A, Small EJ, Spira AI, Vaishampayan UN, Vogelzang NJ, Scheffold C, Ballinger MD, Schimmoller F, Smith DC. Cabozantinib (XL184) in metastatic castration resistant prostate cancer (mCRPC): results from a Phase 2 randomized discontinuation trial. *J Clin Oncol*. 2011; 29 (suppl; abstr 4516).
23. Mattes D, Haynor DR, Vesselle H, Lewellen TK, Eubank W. PET-CT image registration in the chest using free-form deformations. *IEEE Trans Med Imaging*. 2003; 22:120–128. [PubMed: 12703765]

24. Cachier P, Pennec X, Ayache N. Fast non rigid matching by gradient descent: study and improvements of the “demons” algorithm. Research Report 3706, INRIA, June 1999. Available at: <http://hal.inria.fr/docs/00/07/29/62/PDF/RR-3706.pdf>.
25. Yoo, TS.; Ackerman, MJ.; Lorensen, WE.; Schroeder, W.; Chalana, V.; Aylward, S., et al. Engineering and algorithm design for an image processing API: a technical report on ITK—the Insight Toolkit. In: Westwood, JD.; Hoffman, HM.; Mogel, GT., editors. Medicine Meets Virtual Reality. Amsterdam: IOS Press; 2002. p. 586-592.
26. Rossing N, Munck O, Nielsen SP, Andersen KW. What do early bone scans tell about breast cancer patients? Eur J Cancer Clin Oncol. 1982; 18:629–636. [PubMed: 6889965]

Fig. 1. Atlas images for anterior and posterior scans. Anatomic labels for segmentation are shown: extremities (blue), pelvis (green), ribs and head (red), sternum and spine (yellow).

Fig. 2.

Normalization of pixel intensities allows for improved quantitative assessment of change: (a) original bone scans from a single patient at two time points showing variability in overall intensity; (b) normalization of both scans to a standardized atlas intensity; (c) mean receiver operating characteristic curves for the anatomic regions shown (extremities, pelvis, ribs and head, spine) from expert annotated training set of bone scans. Top row, curves generated from anterior-posterior (AP) images. Bottom row, curves generated from posterior-anterior (PA) images.

(a)

(b)

Fig. 3.

Quantitative assessments by the computer-aided treatment assessment system allows for detection of reduction in lesion burden: (a) segmented bone lesions (in red) in a castration-resistant prostate cancer patient are consistent with metastatic foci in the ribs and pelvis on successive scans; (b) *Bone Scan Lesion Count* (blue), *Bone Scan Lesion Area* (red), and *Bone Scan Lesion Intensity* (green) normalized relative to baseline. This example demonstrates the greater sensitivity to change in tumor burden of *Bone Scan Lesion Area* than *Bone Scan Lesion Count*.

Fig. 4. Computer-aided treatment assessment analysis (CADrx) of patient A treated with cabozantinib. (a) Original, intensity-normalized, and CADrx-annotated bone scans from one patient at baseline (top row) and at week 6 after treatment (bottom row). Segmented lesions are shown in each anatomic region: extremities (blue), pelvis (green), ribs and head (red), sternum and spine (yellow). (b) Changes in *Bone Scan Lesion Count*, *Bone Scan Lesion Area*, and *Bone Scan Lesion Intensity* are plotted normalized to their value at screening.

Fig. 5. Computer-aided treatment assessment (CADrx) analysis of patient B treated with cabozantinib. (a) Original, intensity normalized, and CADrx-annotated bone scans from one patient at baseline (top row) and at week 6 after treatment (bottom row). Segmented lesions are shown in each anatomic region: extremities (blue), pelvis (green), ribs and head (red), sternum and spine (yellow). (b) Changes in *Bone Scan Lesion Count*, *Bone Scan Lesion Area*, and *Bone Scan Lesion Intensity* are plotted normalized to their value at screening.

*Excludes one outlier of 315%

Fig. 6. Box and whisker plots showing median (horizontal line), IQR (box) and range, with outliers plotted beyond 1.5 times the IQR from the box, for (a) *Bone Scan Lesion Count*, (b) *Bone Scan Lesion Intensity*, and (c) *Bone Scan Lesion Area*. IQR, interquartile range.

Table 1

Baseline measurements of cabozantinib-treated and untreated patient groups

Median (IQR)	Lesion count (n)	Lesion intensity (AU)	Lesion area (cm ²)
Untreated (n = 10)	42.5 (60.0)	82.7 (23.8)	805.5 (1377)
Cabozantinib-treated (n = 10)	51.5 (29.0)	81.9 (16.6)	385.5 (569)
<i>P</i> value	0.52	0.87	0.82

IQR, interquartile range; AU, arbitrary units.

Table 2

Median (IQR) for the ratio of *Bone Scan Lesion Count*, change in *Bone Scan Lesion Intensity*, and percent change in *Bone Scan Lesion Area*

Median (IQR)	Bone Scan Lesion Count ratio (visit 2/visit 1)	Bone Scan Lesion Intensity (change from baseline)	Bone Scan Lesion Area (percent change from baseline)
Untreated (n = 10)	1.2 (0.6)	−1.4 (14.8)	7.1 (27.6)
Cabozantinib-treated (n = 10)	0.5 (0.7)	−17.6 (16.3)	−73.8 (45.4)
<i>P</i> value	<0.01	<0.01	<0.001

IQR, interquartile range.