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13. ABSTRACT (Maximum 200 Words)

It is generally recognized that ^{111}In capromab pendetide (PS) scans are technically challenging to perform and interpret, particularly with regard to pelvic SPECT studies used to detect possible disease in the prostate fossa and pelvic lymph node (LN). The hypothesis of this proposal is that the superior spatial resolution, high image contrast, and much reduced image artifacts that result from the corrective SPECT image reconstruction methods would substantially aid in the detection and diagnosis of prostate cancer. To test our hypothesis, we propose five specific aims: (1) to develop simulation tools and methods that allow efficient generation of accurate ^{111}In PS projection data from the human pelvic area, (2) to study the effects of 3D image degrading factors on ^{111}In PS SPECT images, (3) to develop 3D corrective image reconstruction methods for ^{111}In PS SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors, (4) to evaluate the 3D corrective image reconstruction methods for clinical ^{111}In PS SPECT studies using simulated patient data, and Hotelling and human observer studies, and (5) to evaluate the clinical efficacy of the corrective image reconstruction methods as applied to ^{111}In PS SPECT using patient data.

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INTRODUCTION

Prostate carcinoma, a leading cause for male cancer deaths, was estimated to result in 180,400 new cases and 31,900 deaths in the year 2000[1]. Earlier detection of prostate cancer has resulted from screening with serum prostate-specific antigen (PSA), with detection of disease when it is more localized[2]. In order to treat prostate cancer appropriately, it is essential to have accurate staging data. Clinicians try to determine tumor size and location, degree of periprostatic extension and whether bone and/or lymph node (LN) metastases are present. Imaging techniques routinely used for this purpose include transrectal ultrasound, pelvic CT and MRI, and radionuclide bone scanning. Despite these efforts, initial evaluation of pre-surgical patients leads to understaging in as high as 40 to 71% of patients[3]. Detection of LN metastases has been difficult, since LN involvement in prostate cancer is often associated with normal sized nodes. Since detection of LN disease with pelvic CT and MRI depends upon LN enlargement, neither of these modalities has been very successful in detecting the spread of prostate cancer to nodes (MRI slightly better than CT). Pooled data from four MRI series demonstrate an overall sensitivity of 42% and specificity of 98% [4].

Imaging with ^{111}In capromab pendetide (PS), a monoclonal antibody agent utilizing an indium-labeled antibody to prostate-specific membrane antigen (present in increased amounts in prostate cancer cells) has proven useful in detecting LN metastases. It is particularly useful in the detection of recurrent prostate carcinoma in patients who have had radical prostatectomy for their disease, but who have increasing PSA levels indicating the presence of an additional tumor. In a multi-institutional study, ^{111}In PS scanning localized disease in 108 of 181 patients (60%) with uptake in the prostatic fossa in 62 patients (34%), pelvic LN in 40 patients (22%) and abdominal LN in 42 patients (23%)[5]. Results were evaluated for the prostate fossa by ultrasound guided biopsy: 59 patients had positive biopsies for recurrent tumor, but only 29 of these had positive scans for a sensitivity of 49%[6]. The investigators felt that the false negative scans were likely to be due to small tumor volume. Results are more difficult to confirm for disease outside the prostatic fossa, since the LN metastases will usually be too small for detection by CT or MRI.

It is generally recognized that ^{111}In PS scans are technically challenging to perform and interpret[5], particularly with regard to the pelvic SPECT study used to detect possible disease in the prostate fossa and pelvic LN. Certainly part of this challenge is the detection of increased uptake in relatively small tumors in the pelvis.

In our preliminary study, we have demonstrated that corrective image reconstruction techniques that accurately correct for attenuation, collimator-detector response and scatter can significantly improve the quality and quantitative accuracy of ^{111}In PS SPECT images. The hypothesis of this proposal is that the superior spatial resolution, high image contrast, and much reduced image artifacts that result from the corrective SPECT image reconstruction methods would substantially aid in the detection and diagnosis of prostate cancer.

To test our hypothesis, we propose five specific aims: (1) to develop simulation tools and methods that allow efficient generation of accurate ^{111}In PS projection data from the human pelvic area, (2) to study the effects of 3D image degrading factors on ^{111}In PS SPECT images, (3) to develop 3D corrective image reconstruction methods for ^{111}In PS SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors, (4) to evaluate the 3D corrective image reconstruction methods for clinical ^{111}In PS SPECT studies using simulated populations of patient data, and Hotelling and human observer studies, and (5) to evaluate the clinical efficacy of the corrective image reconstruction methods as applied to ^{111}In PS SPECT using patient data.

BODY

One of the major events during the first year of the project is the relocation of our laboratory from the University of North Caroline at Chapel Hill (UNC-CH) to Johns Hopkins University (JHU) in July 1, 2002. We planned the move very carefully. With the cooperation of both administrations of UNC-CH and JHU, the relocation and transfer were extremely smooth and we only had to close down the laboratory for only about one week during the move. The major hold up after we started at JHU is the IRB approval of the clinical ^{111}In PS prostate SPECT study. Due to changes in IRB at JHU in the Fall of 2002, the submission and reviewed our IRB application was delayed till late Fall. We were notified by the IRB in late December requesting clarifications about the use of the new GE VG SPECT system with the Hawkeye x-ray unit. In the mean time, the study protocol using the new GE VG SPECT system with the Hawkeye x-ray unit was accepted as a routine clinical protocol. Instead of requesting for IRB approval, we applied for IRB exemption which was approved on February 27, 2003. As a result, we are approved to proceed with the clinical research project as of February 27, 2003.

In the following, we describe the progress we have made during Year 1 of the project. The report addressesthe specific tasks for Year 1 listed in the original proposal.

Task 1. *To develop simulation tools and methods for ^{111}In prostate SPECT (Months 1-18):*

a. *Extend the realistic NCAT phantom to include the pelvic region of the body (Months 1-12)*
b. *Continue the development of a Monte Carlo simulation method that generates realistic projection data from the NCAT phantom with accurate models of the multiple photon emissions from ^{111}In, their attenuation and scatter in the body, and the geometric, penetration and scatter response of the collimator (Months 4-18)*

Accomplishments:

1. We have completed Task 1a of the original proposal. The 3D NCAT (NRUB-based CArdiac Torso) phantom developed in our laboratory was extended for use in the project. Figure 1 shows the standard 3D NCAT phantom recently developed in our laboratory under the support of a separate NIH grant. Figure 2 shows the extension of the 3D NCAT phantom developed under the support of the present DOD research grant. Figure 3 shows the detailed anatomical structures including the prostate, bladder, key blood vessels and the 26 lymph nodes in the pelvic region of a male patient. Figure 4 shows sample slices through the phantom showing the simulated distribution of ^{111}In PS in the pelvic region that is based on clinical studies. Figure 5 shows the corresponding image slices showing the attenuation coefficient distribution.
2. We have made significant progress of Task 1b of the original proposal. We have successfully tested the MCNP Monte Carlo code that will be used in the research. Specifically, we implemented the extended 3D NCAT phantom in the MCNP code to generate list mode data of photons that were emitted from source distributions within the phantom, experienced photoelectric, scatter or no interaction with the tissue material of the phantom, and emerged from the surface of the phantom. In order to accurately simulate the response function of the medium collimator that are used in acquiring In-111 PS data, Monte Carlo simulation of photons through the collimator that include the effects of penetration and scatter within the collimator is desirable. However, Monte Carlo simulation in both the phantom and collimator is extremely time-consuming even using the 90-node computer cluster in our

laboratory.

Instead, we are developing a technique that pre-determine the collimator-detector response (CDR) function that includes the geometric, penetration and scatter components in a look-up table. The final projection data of the phantom will be obtained by reading the listmode data and run through the 3D CDR look-up table. The use of the look-up table provide a saving of computational time by a factor of over 100.

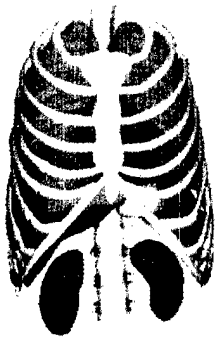

Figure 1. The standard 3D NCAT phantom

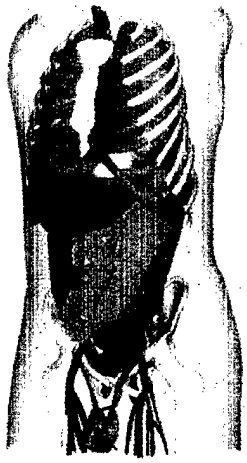

Figure 2. Extension of the 3D NCAT phantom to include the pelvic region.

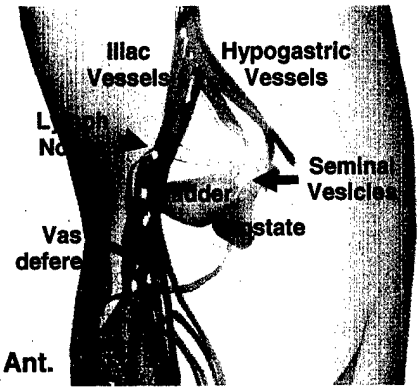

Figure 3. Detail anatomical structures included in the extended NCAT phantom.

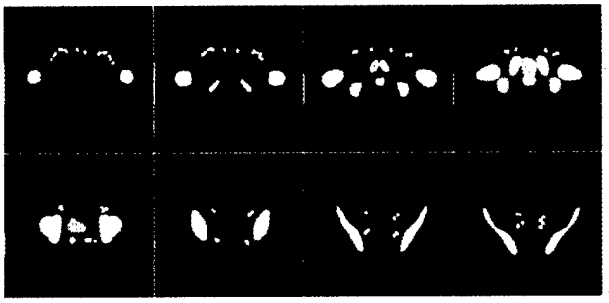

Figure 4. Sample slices through the pelvic region of the extended 3D NCAT phantom showing In-111 PS distribution. The slice thickness is 3.2 mm and the sample slices are selected every 8th slice from the complete set.

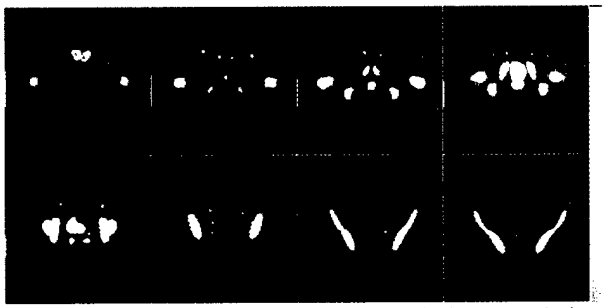

Figure 5. Corresponding slices through the extended 3D NCAT phantom as shown in Figure 4 showing the attenuation coefficient distribution.

Task 2. *To study the effects of 3D image degrading factors on ^{111}In prostate SPECT (Months 4-21):*

a. *Study the effect of photon attenuation in the patient's body on ^{111}In SPECT images (Months 4-12)*
b. *Study the effects of photon scatter in patient's body on ^{111}In SPECT images (Months 7-15)*
c. *Study the effects of collimator-detector response on ^{111}In SPECT images (Months 10-18)*

We have begun the study of the effects of 3D image degrading factors on ^{111}In prostate SPECT imaging. As discussed in Task 3 below, we have developed and implemented corrective image reconstruction methods for ^{111}In prostate SPECT. The process allows us to study the effects of the degrading factor on the reconstructed images. For example, Figure 6 shows the

reconstructed images from a patient study obtained using different corrective image reconstruction methods. Images on the left-most column were obtained from using the filtered backprojection (FBP) without any correction of the image degrading factors. Images on the right-most column were obtained using the OS-EM algorithm with correction of the CDR, attenuation and scatter in the patient. The result is closest to the true ^{111}In PS distribution. Images on the column second to the right-most column were obtained using the OS-EM algorithm with correction of the CDR and attenuation in the patient. They indicate the effect of scatter alone on the reconstructed images. Images on the column third to the right-most column were obtained using the OS-EM algorithm with correction of the CDR alone. They demonstrate the combined effects of attenuation and scatter in the patients on the reconstructed images.

Since we do not know the truth distribution in a patient study, the best method to study the effects of the image degrading factors is through simulation study. We are in the process of applying the extended 3D NCAT phantom and the simulation tools developed in Task 1 to study the effects of the degrading factors in more detail.

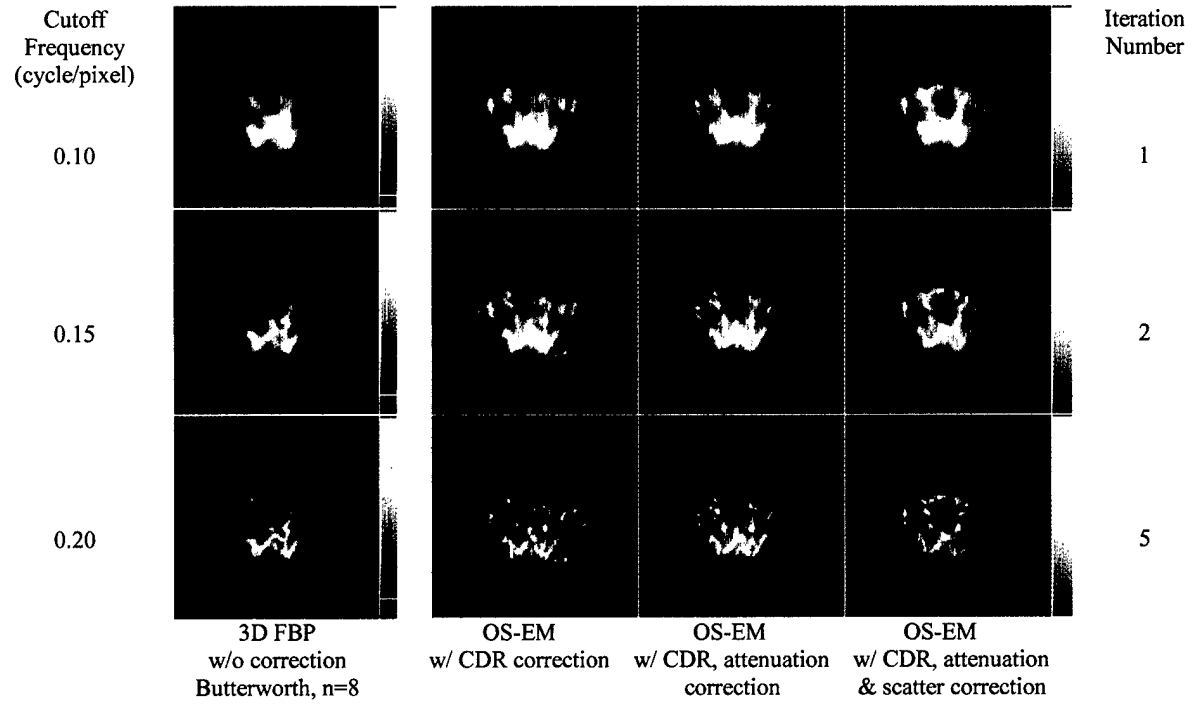

Figure 6. Reconstructed images from a patient study obtained using different corrective image reconstruction methods. *Left-Most Column:* Images were obtained from using the filtered backprojection (FBP) without any correction of the image degrading factors. *Second Column from the Left:* Images obtained using the OS-EM algorithm with correction of the CDR alone. *Third Column from the Left:* Images obtained using the OS-EM algorithm with correction of the CDR and attenuation in the patient. *Right-Most Column:* Images obtained using the OS-EM algorithm with correction of the CDR, and attenuation and scatter in the patient.

<u>Task 3.</u> *To continue the development of 3D corrective image reconstruction methods for ^{111}In prostate SPECT that provide much improved image quality and quantitative accuracy by incorporating models of the 3D image degrading factors (Month 7-24):*

a. To use results from Task 2 to guide the development of methods to incorporate accurate models of image degrading factors in iterative and non-iterative 3D image reconstruction methods (Months 7-24)

We have made significant progress in accomplishing Task 3a. The corrective image reconstruction methods that are under development are based on iterative image reconstruction algorithms. As shown in Figure 7, a typical iterative reconstruction algorithm allows one to incorporate models of the imaging process in the projection and backprojection steps. Through the iterative process, accurate compensation of the effects of imaging degrading factors can be achieved.

We completed the implementation of accurate models of the collimator-detector response (CDR), and attenuation and scatter in the iterative ordered-subset expectation-maximization (OS-EM) image reconstruction algorithm to correct for their effects. Figure 8 shows the different components of CDR found in medium- and high-energy collimators at different energies. Typical experimental measured point response functions from these collimators are shown in Figure 9. We incorporate accurate model of the CDR of the collimator as a function of source distances in the OS-EM algorithm as shown in Figure 7. To compensation for photon attenuation, we incorporate the attenuation distribution of the patient obtained from transmission CT studies. For scatter compensation, we apply the effective scatter source method as shown in Figure 10 developed in our laboratory.

Figure 6 shows preliminary results from applying the corrective image reconstruction to a clinical ^{111}In PS prostate SPECT study. They indicate the substantial improvement in image quality using the corrective image reconstruction methods especially when all the image degrading factors, i.e., CDR, and attenuation and scatter in the patient, are included in the correction.

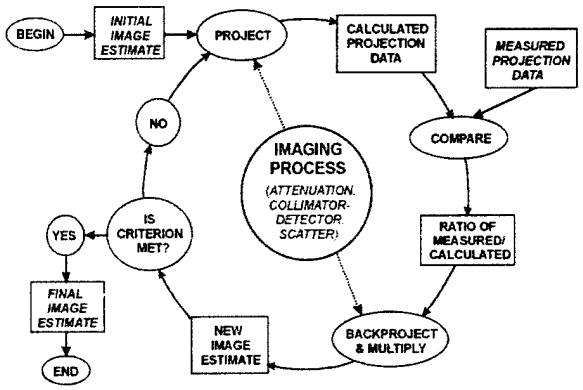

Figure 7. Corrective image reconstruction using iterative image reconstruction algorithms. Accurate models of the imaging process including the collimator-detector response (CDR) and attenuation and scatter in the patient can be incorporated in the iterative reconstruction algorithm to compensate for their effects.

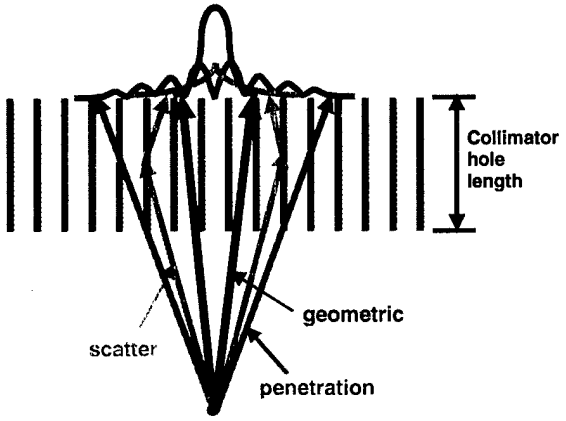

Figure 8. Components of collimator-detector response (CDR). For ME and HE collimator using ME and HE collimators, the penetration and scatter components are significant as compared to the geometric component.

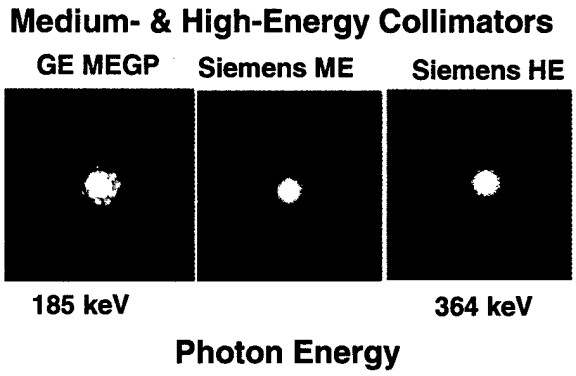

Figure 9. Measured point response function of different medium- and high-energy collimators

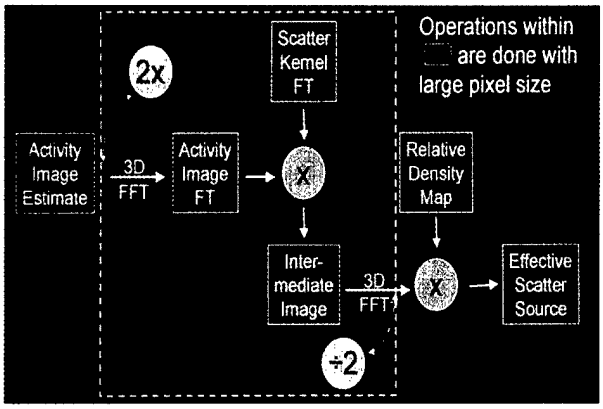

Figure 10. Scatter correction methods based on effective scatter source that can be implemented in iterative image reconstruction methods.

KEY RESEARCH ACCOMPLISHMENTS

1. Completed extension of the realistic 3D NCAT phantom to include the pelvic region of the body. The extended phantom includes the prostate gland, bladder, key blood vessels and major lymph nodes in the pelvic region.

2. Made significant progress in applying the MCNP Monte Carlo simulation code to the extended 3D NCAT phantom to generate simulate accurate SPECT projection data. A key component of the development is a method to utilize a pre-determined 3D look-up table using Monte Carlo method to substantially (over 100-folds) improve the computational time involved in the simulation.

3. Study the effects of CDR, and attenuation and scatter on ^{111}In PS prostate SPECT images.

4. Developed and implemented corrective image reconstruction methods that incorporate accurate models of CDR and attenuation and scatter in the patient for substantial improvement in ^{111}In PS prostate SPECT image quality.

5. Applied the corrective image reconstruction methods in #4 in preliminary clinical study.

REPORTABLE OUTCOMES

Abstracts

1. Tsui BMW, Zhao XD, Segars WP, Sayeram S and Frey EC. Quantitative In-111 Prostascint SPECT Imaging with Fusion with Anatomical Information. 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

2. Tsui BMW, Du Y, Segars WP, Zhao X and Frey EC. Fast Monte Carlo Simulation Methods for Medium- and High-Energy SPECT. 2002 IEEE Nuclear Science Symposium and Medical Imaging Conference, Norfolk, VA, November 10-16, 2002.

3. Garrity J, Segars WP and Tsui BMW. Development of a Dynamic Model for the Lung Lobes and Airway Tree in the NCAT phantom, 2002 IEEE Nuclear Science Symposium and Medical Imaging Conference, Norfolk, VA, November 10-16, 2002.

Presentations

1. Tsui BMW, Zhao XD, Segars WP, Sayeram S and Frey EC. Quantitative In-111 Prostascint SPECT Imaging with Fusion with Anatomical Information. Presented at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, CA, June 15-19, 2002.

2. Tsui BMW, Du Y, Segars WP, Zhao X and Frey EC. Fast Monte Carlo Simulation Methods for Medium- and High-Energy SPECT. Presented at the 2002 IEEE Nuclear Science Symposium and Medical Imaging Conference, Norfolk, VA, November 10-16, 2002.

Manuscripts

1. Garrity J, Segars WP and Tsui BMW. Development of a Dynamic Model for the Lung Lobes and Airway Tree in the NCAT phantom, in Conference Record of the 2002 IEEE Nuclear Science Symposium and Medical Imaging Conference, Norfolk, VA, November 10-16, 2002, in press.

CONCLUSIONS

We have made significance progress in Year 1 of the project. The 3D NCAT phantom was fully extended to include the prostate, major blood vessels and lymph nodes in the pelvic region. The phantom was successfully implemented in the MCNP Monte Carlo code to generate list mode data of photons that were emitted from source distributions within the phantom, experienced photoelectric, scatter or no interaction with the tissue material of the phantom, and emerged from the surface of the phantom. We are working on a method that utilizes a pre-determined 3D look-up table using Monte Carlo method to substantially (over 100-folds) improve the processing time involved in the simulation. The simulation tools are important in the simulation studies to be carried out in Years 2 & 3 of the project.

We have begun a study of the effects of collimator-detector response (CDR), and attenuation and scatter in the patient on ^{111}In PS prostate SPECT images. Preliminary study using patient data and corrective image reconstruction methods demonstrate the image degradation due to different combinations of CDR, attenuation and scatter on ^{111}In PS prostate SPECT images. The preliminary results will provide guidance in more detailed simulation studies to investigate these effects to be carried out in Year 2 & 3 of the project.

We have made significant progress in the development of corrective image reconstruction methods for ^{111}In PS prostate SPECT. The methods are based on iterative image reconstruction methods that incorporate accurate models of the 3D CDR, and attenuation and scatter in the patient. The corrective image reconstruction methods were successfully implemented using the iterative OS-EM algorithm. Preliminary results using clinical data demonstrate dramatic improvement in image quality.

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