Clinical Utility of Temporal Subtraction Images in Successive Whole-Body Bone Scans: Evaluation in a Prospective Clinical Study

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In order to aid radiologists' routine work for interpreting bone scan images, we developed a computerized method for temporal subtraction (TS) images which can highlight interval changes between successive whole-body bone scans, and we performed a prospective clinical study for evaluating the clinical utility of the TS images. We developed a TS image server which includes an automated image-retrieval system, an automated image-conversion system, an automated TS image-producing system, a computer interface for displaying and evaluating TS images with five subjective scales, and an automated data-archiving system. In this study, the radiologist could revise his/her report after reviewing the TS images if the findings on the TS image were confirmed retrospectively on our clinical picture archiving and communication system. We had 256 consenting patients of whom 143 had two or more whole-body bone scans available for TS images. In total, we obtained TS images successfully in 292 (96.1%) pairs and failed to produce TS images in 12 pairs. Among the 292 TS studies used for diagnosis, TS images were considered as "extremely beneficial" or "somewhat beneficial" in 247 (84.6%) pairs, as "no utility" in 44 pairs, and as "somewhat detrimental" in only one pair. There was no TS image for any pairs that was considered "extremely detrimental." In addition, the radiologists changed their initial reported impression in 18 pairs (6.2%). The benefit to the radiologist of using TS images in the routine interpretation of successive whole-body bone scans was significant, with negligible detrimental effects.

KEY WORDS: Bone scintigram, whole-body scan, interval change, temporal subtraction image, prospective clinical study

INTRODUCTION

Bone scintigraphy is one of the most common nuclear medicine examinations.^{1,2} Successive bone scans are commonly used for monitoring of a patient's response to therapy and also detection of new lesions in successive examina-

tions, because bone scans are generally more sensitive to bone pathology than are conventional radiography and CT. However, it is time-consuming to identify multiple lesions such as bone metastases of prostate and breast cancers, and it is difficult to detect subtle changes between two successive abnormal bone scans because of variations, in successive examinations, in patient conditions, radioisotope distributions, and technical factors such as patient positioning and the use of different gamma cameras and settings. Although there were several digital image-processing techniques for quantifying lesion uptake such as digital subtraction³ and signal-to-noise ratio, the quantification of interval changes has been challenging task for radiologists.

In order to assist radiologists in interpreting whole-body bone scans, we developed a computerized temporal subtraction (TS) technique which

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can highlight interval changes between successive whole-body bone scans.⁴ We have previously demonstrated the usefulness of TS images in terms of the reduction of reading time and improvement in diagnostic accuracy for identifying interval changes by carrying out an observer performance study.⁵ Here, we performed a prospective clinical study for evaluating the clinical utility of TS images in successive whole-body bone scans.

MATERIALS AND METHODS

Bone Scan Examination

In bone scan examinations, the patient was injected with one of two radiopharmaceuticals of technetium^{99m} methylene diphosphonate (Tc^{99m}-MDP) or technetium^{99m} hydroxymethane diphosphonate (Tc^{99m}-HDP) and returned after 2 to 3 h for imaging. We used three different gamma cameras for obtaining whole-body bone scans. They were IRIX (Picker, Cleveland, OH, USA), Skylight (Philips, Cleveland, OH, USA), and BrightView (Philips, Cleveland, OH, USA, since October 2008). Standard viewing of all bone scan images was performed by use of the standard picture archiving and communication system (PACS; Stentor/Philips iSite, Amsterdam, The Netherlands).

Computerized Scheme for Producing TS Images

Our computerized scheme for producing TS images between two successive whole-body bone scans consisted of three steps⁴: (1) normalization of the gray scale of each image by use of the average pixel values of the normal bone structure (i.e., skull, spine, joints, ribs, and long bones); (2) matching of the image size, orientation, and gray scale of the previous image to those of the current image; and (3) application of a nonlinear image-warping technique based on elastic matching⁶ for accurate registration of the two images. Figure 1 shows one example of (a) a pair of the original previous and current images presented on the standard PACS viewer and (b) a pair of the modified previous and current images and a TS image obtained by use of this computerized scheme. In the case illustrated, numerous lesions are present in both previous and current images,

and they include both hot (progressive) and cold (retrogressive) interval changes. It is more time-consuming and difficult to characterize them on the original images without than with a TS image.

Prospective Clinical Study

Before we started our prospective clinical study, we developed a TS image server which included five additional functions: (1) an automated image-retrieval system for searching the most recent whole-body bone scan images in PACS; (2) an automated image-conversion system for converting several types of image formats into raw image data with a 256×1,024 matrix size; (3) an automated TS image-production system; (4) a computer interface for displaying and evaluating TS images together with the routine diagnosis by use of the PACS; and (5) an automated data-archiving system by securing patient identification.

This clinical study was approved by the institutional review board of our institution. With this approval, we used the TS images of a patient only when we obtained his/her consent. The radiologist could revise his/her report after reviewing the TS images if the findings on the TS images were confirmed retrospectively in the study on our clinical PACS.

Figure 2 shows the steps involved in conducting this clinical study. The radiologist first determined whether consent from each patient was given or not. If consent was obtained, TS images were prepared automatically by the TS server by entering of the patient ID in the computer. It took 5–10 min for computing TS images in each case.

In the standard reading without TS images, the radiologist made his/her initial decision regarding bone-scan scintigrams by using a standard PACS viewer (Stentor) as usual and dictated the findings (or reviewed with a resident to dictate). At this step, the radiologist did not sign/finalize his/her report until he/she had viewed the TS images. Following the standard reading, the radiologist was required to read the case again along with the TS images immediately after the completion of the initial reading if the TS images were available for viewing. In cases where the TS images were not immediately available following the initial clinical read, the radiologist was allowed to review them at his/her earliest convenience. During the second

Fig. 1. Example of a pair of the original previous and current images and b the modified and warped previous images, and a modified current image and a TS image obtained by use of this computerized scheme.

reading with the TS images, the radiologist referred to his/her original assessments in order to confirm his/her impression from the TS images.

Immediately after the second reading, in order to evaluate the clinical utility of TS images, we asked the radiologist a question concerning the overall utility of TS images by using a discrete five-point scale (i.e., extremely beneficial, somewhat beneficial, no utility, somewhat detrimental, and extremely detrimental). In addition, the overall utility was evaluated and graded with a number of reasons such as “change in impression,” “increase/

decrease in confidence,” “change in findings,” or “the potential to increase/reduce the reading time.” It should be noted that the radiologists were asked to identify only the interval changes related to malignant lesions which were visible on the original images viewed with use of the standard PACS; they did not include other interval changes considered due to benign etiology such as osteoarthritis and fractures. In addition, when the radiologist provided any responses except for “no utility,” he/she was asked to mark the positions of the relevant interval changes (if he/she found them because of the use of TS images) and to select one of five reasons. Among the five reasons, three are related to characteristics of marked interval changes (new bone lesion, change in bone lesion, or soft-tissue change), and two are related to whether a case has interval changes or no interval change. Moreover, in order to estimate the utility of TS images in terms of actual clinical actions, we also asked the radiologist whether the use of TS images changed his/her original impression in the report. However, in order for the radiologist to change the original report following a review of the TS images, we asked him/her to confirm his/her judgment by using the clinical PACS for viewing the original whole-body bone scans as well as static spot images of lesions of interest.

Fig. 2. Diagram for the steps involved in this clinical study.

Retrospective Confirmation

In order to confirm that the changes in the impression made during the prospective study were not adversely affected by use of TS images, a consensus was made for all corresponding cases retrospectively by a panel of two radiologists who specialized in nuclear medicine.

RESULTS

The prospective study was performed between November 22, 2006 and November 30, 2008 in our hospital. We had 256 consenting patients of whom 143 had one or more pairs of whole-body bone scans available for TS images. For the 143 patients with consent, there were 304 pairs of bone scans. We obtained TS images successfully in 292 (96.1%) pairs and failed to produce TS images in 12 pairs. There was one pair of whole-body bone scans available for TS images in 69 patients, two pairs for 28, three for 26, four for nine, and five or more for 11 ($n=304$). The average number of pairs available for TS images per patient was 2.1, and the maximum number of pairs was eight during the period of our prospective study.

Radiologists' subjective ratings for the clinical utility of TS images applied to the 292 pairs of successive bone scans in this prospective study indicated that TS images were considered as "extremely beneficial ($n=24$)" or "somewhat beneficial ($n=223$)" in 247 (84.6%) pairs of successive bone scans, whereas they were considered as having "no utility" in 44 pairs and as "somewhat detrimental" in only one pair. There was no case considered "extremely detrimental."

For 247 TS images for pairs of successive bone scans, which were considered as "extremely beneficial" or "somewhat beneficial," major reasons for radiologists' positive feedback were "TS image increased radiologist's confidence in his/her original assessment" (102, 41.3%) and "TS image increased radiologist's confidence for no change in successive scans" (89, 36.0%). Figure 3 shows one example which was considered as "somewhat beneficial" because the radiologist's confidence in his/her original assessment was increased by use of TS images.

New bone lesions and changes in bone lesions were discovered only after use of the TS images in

28 (11.3%) and 28 (11.3%) pairs of successive bone scans, respectively. Figure 4 shows one example which was considered as "extremely beneficial" because a new bone lesion was discovered by use of TS images. Soft tissue findings were discovered only after the use of TS images in three (1.2%) pairs. Note that the sum of these numbers of pairs became 250 because two reasons for radiologists' positive feedback were reported in three pairs of successive bone scans.

The radiologists changed the final impression of their initial report in 18 pairs of successive bone scans (6.2%). The changes of their impression made by use of TS images were retrospectively confirmed as "correct responses" by the consensus of two expert radiologists. Figure 5 shows (a) a case with nine sequential whole-body bone scans and (b) eight TS images for each pair of successive bone scans obtained in this prospective clinical study. Two of the eight TS images (the 1st and 5th) were considered as "extremely beneficial," and the initial report was changed at the time of the 1st TS image trial. The remaining six TS images were considered as "somewhat beneficial" in five instances and "no utility" in one instance.

DISCUSSION

The clinical utility was considered as "extremely beneficial" or "somewhat beneficial" for the majority of TS images. Even though most interval changes on the successive whole-body bone scans could be identified by radiologists, TS images could be used as a "second opinion" for most cases regardless of whether the initial interpretation identified an interval change. In addition, for some extremely subtle lesions, TS images could remind the radiologist to re-review the images. In this study, radiologists changed their final impression in their report in 18 (6.2%) pairs of successive bone scans following a review of the TS images.

Figure 6 shows the only pair of successive bone scans in which TS images were considered "somewhat detrimental" in this prospective study. Although the vast majority of misregistration artifacts on TS images were easily distinguished from actual interval changes by radiologists, this false-positive uptake at the right sacroiliac joint on TS was regarded as a likely new interval change

Fig. 3. Metastasis evaluation in a 48-year-old woman with recurrent ovarian carcinosarcoma. The initial bone scan showed no bone metastases. Follow-up scan showed a single subtle new metastasis at the inferior left sacroiliac joint. This would easily be overlooked on the scan alone but became quite obvious on the TS images (*arrow*).

until the radiologist confirmed that there was no interval change in this location by use of other information such as spot views and CT on the clinical PACS.

We failed to produce TS images for 12 pairs of successive bone scans because of (1) missing raw image data for a previous examination (seven

pairs), (2) inadequate imaging condition (three pairs), and (3) improper positioning of the patients (arms up or prone position; two pairs).

Almost all workstations for whole-body bone scans or other nuclear-medicine imaging have the function of maintaining and/or adjusting a gray scale of image properly. However, this function

Fig. 4. Sixty-nine-year-old man with prostate carcinoma. The initial bone scan demonstrated multiple bone metastases. The follow-up scan was initially interpreted as stable disease. However, the TS images demonstrated an obvious single new anterior right iliac lesion (confirmed on CT) which was initially missed given the multiple stable lesions elsewhere (*arrow*).

Fig. 5. Sixty-four-year-old man with widely metastatic prostate carcinoma. (a) Many serial bone scans performed with various gamma cameras result in images with differences in patient size, position, and intensity. (b) Once normalization and temporal subtraction were performed, changes over time became obvious, including initial significant improvement and later subtle progression at the left SI region (arrow).

was usually applied to each view or each examination but was not normalized for successive examinations. Therefore, the display condition of nuclear-medicine images such as the gray scale (level and contrast), and the magnification factor was not consistent for all cases. Because our computerized method matched gray scales of previous and current images by use of intensity levels on normal skeletal structures and matched sizes and inclinations by use of the length between head and toe and a mid-line of patient projections, radiologists easily recognized interval changes

compared to those displayed on the standard PACS.

There are some limitations of our TS imaging. With use of TS images, interval changes on successive images were represented by black or white for progressive and retrogressive lesions, respectively. However, as shown in Figure 7, a progressive lytic (as opposed to the more typical sclerotic) lesion was represented as white. In addition, the use of TS images would have possible disadvantages due to the specific characteristics of bone scans. For example, the radio-

Fig. 6. Metastasis evaluation in a 25-year-old woman with breast cancer status post craniotomy. The follow-up bone scan was initially interpreted as stable with no metastatic disease. However, the TS images demonstrated a linear focus at the right SI region (*arrow*) suggesting interval tumor or insufficiency fracture. After careful review of the original scans, however, no abnormalities were identified and this was deemed an unusual artifact, resulting in prolonged interpretation time and decreased reader confidence.

active urine liquid contamination on body surface and radioactive leakage of injection dot could be incorrectly diagnosed as abnormal lesions. Although the change of patient's body shape and/or inconsistent patient's positioning in the successive bone scan could be adjusted by the nonlinear

warping technique, they could produce quasi-interval changes. Therefore, sufficient knowledge for lesion diagnosis should be required for radiologists who use TS images.

An additional limitation on this prospective study is that there was uncertainty about reference

Fig. 7. Sixty-six-year-old man with renal cell carcinoma. Initial bone scan demonstrated several metastases including a mixed lytic-sclerotic lesion in the right posterior eighth rib. On the follow-up scan, there had been progression of the lytic component of this lesion, evident in white on the TS images (*arrow*).

standards for interval changes. An appropriate therapeutic procedure was performed on a patient when interval changes on successive images were found and reported; thus, the patient's conditions changed over time, and it was difficult to establish whether all interval changes reported were correct or not.

In conclusion, the usefulness of TS images in successive whole-body bone scans was demonstrated in terms of its clinical utility in this prospective clinical study. The TS image could, with negligible detrimental effects, be used as a "second opinion" for radiologists; thus, it could increase their accuracy, speed, and confidence in the interpretation of whole-body bone scans.

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