An Improved Method for Quantitative Bone Scanning

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A quantitative gamma-camera technique is used to calculate the percentage of administered activity taken up by various areas of the skeleton. The method uses an external standard source of activity as a reference, and in addition presents the information in a new format, the Organ Uptake Image (OUI). Two cases of Paget's disease serve to illustrate the usefulness of this approach to quantitative bone imaging.

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The discovery of bone-seeking compounds that can be labeled with technetium-99m has increased the clinical application of bone scanning. In 1971 it was demonstrated that Tc-99m tripolyphosphate had an affinity for bone mineral, which led to the introduction of phosphorus compounds as skeletal imaging agents (*1*). The following year, others found that Tc-99m-labeled phosphonates had similar bone-seeking properties (*2–4*). These advances, coupled with improvements in imaging equipment, fostered the adoption of qualitative bone scanning as the primary means for detecting many kinds of bone disease (*5*). However, if studies of the same patient are done at different times, qualitative representations of tracer distribution can suggest changes unrelated to the patient's condition. These differences may be due to technical variations associated with radiopharmaceutical quality, instrument performance, and/or film processing.

To provide for more accurate interpretation, investigators have considered quantitative approaches that would minimize the effects of technical factors on scan interpretations. Instead of recording analogue images, one can accumulate fixed-time digital images with appropriate equipment interfaced to a gamma camera, producing data that can be analyzed in a number of ways.

Quantitative methods up to the present have emphasized the use of activity ratios between abnormal and normal bone (*6–11*). The normal bone serves as an internal standard for comparison with areas of disease. To accomplish this, one can display the image on an oscilloscope, select regions of interest (ROIs) on the skeleton with a light pen, derive the number of counts in each ROI, and then compute activity ratios between abnormal and normal bone. A more sophisticated method permits estimation of the percentage of the administered activity taken up in each ROI by comparison of the ROI counts with the counts from an external standard source of activity placed in a scattering phantom. The reproducibility of the method has been established (Castronovo, F, in preparation), and it is this technique to which our current approach is applied.

MATERIALS AND METHODS

Castronovo gives the expression for percentage uptake by an ROI:

$$\%\ \text{uptake} = \left(\frac{\text{ROI counts}}{\text{ROI cells}} - \frac{\text{BKG counts}}{\text{BKG cells}}\right)(\text{ROI cells})\left(\frac{\text{EXT STD activity}}{\text{EXT STD counts}}\right)\left(\frac{100}{\text{PT dose}}\right).$$

In this equation, "cells" refers to the number of picture elements in the ROI portion of the oscilloscope matrix. "BKG" refers to background in an ROI in soft tissue, one of which is chosen in each frame of the study. (The selection of background ROIs is discussed below). The expressions, $\frac{\text{EXT STD activity}}{\text{EXT STD counts}}$ and $\frac{100}{\text{PT dose}}$, are decay-corrected. Use of the equation also requires inclusion of decay correction factors necessary to refer all uptakes to the same point in time.

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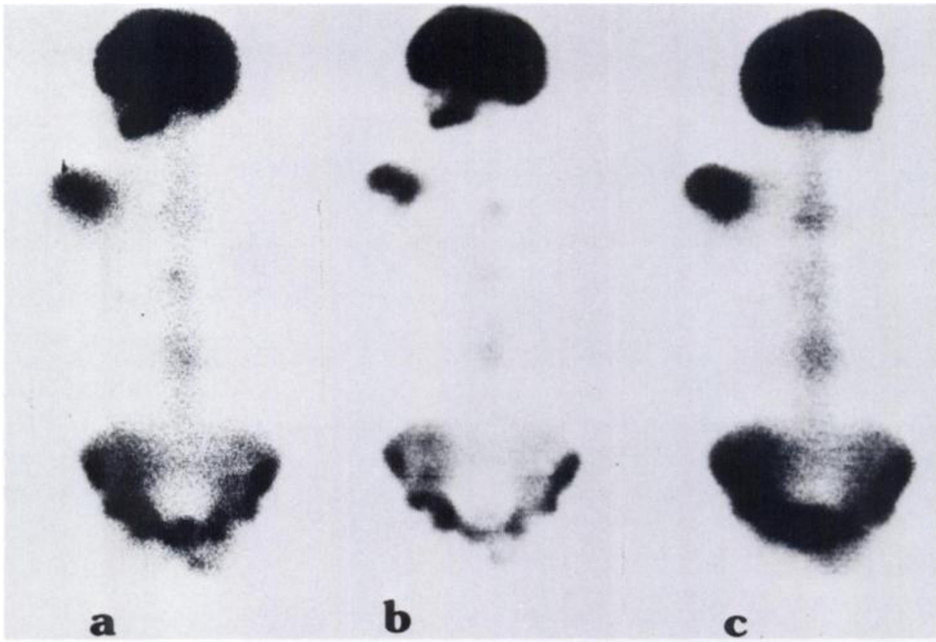

FIG. 1. Case 1, rectilinear bone scans, anterior view: (a) 3 mo, (b) 9 mo, and (c) 15 mo after the start of therapy. For all three scans, enhancement = 0 and window = 140 ± 40 keV. For a and b, scan speed = 1,000 cm/min and bkg. erase = 3. For c, scan speed = 900 cm/min and bkg. erase = 5. For a, b, and c, the peak counts and intensity were respectively 90K and 30, 200K and 25, and 60K and 32.

One may not always flag the same number of cells for a given ROI on serial studies of the same patient. Dividing % uptake by ROI cells produces a % uptake/cell independent of the exact number of cells included in the ROI. Dividing further by the % uptake/cell of an ROI consisting of apparently normal bone (internal standard) accounts for day-to-day variations in the patient's metabolism of the imaging agent.

Instead of expressing uptakes numerically, one can take the number of counts stored in some selected cell in the raw image, subtract the BKG counts per cell, multiply by $\frac{\text{EXT STD activity}}{\text{EXT STD counts}}$ and $\frac{100}{\text{PT dose}}$ (both decay-corrected), and store the result in the cell in place of the original number of counts. The cell now stores approximately the percentage of the administered dose seen in that picture element. This calculation can be performed for each cell of a raw image, and when the result is displayed on the oscilloscope, the new image will represent approximate percentage uptake rather than raw counts. We call this an Organ Uptake Image (OUI).

No allowance has been made in these calculations for internal tissue absorption, which may introduce significant error in calculating *absolute* uptakes. When comparing the same ROIs or OUIs from serial studies, however, these calculations will yield an accurate estimate of differences in uptake, assuming the tissue absorption to be similar for any given area of the image. The results are nevertheless re-

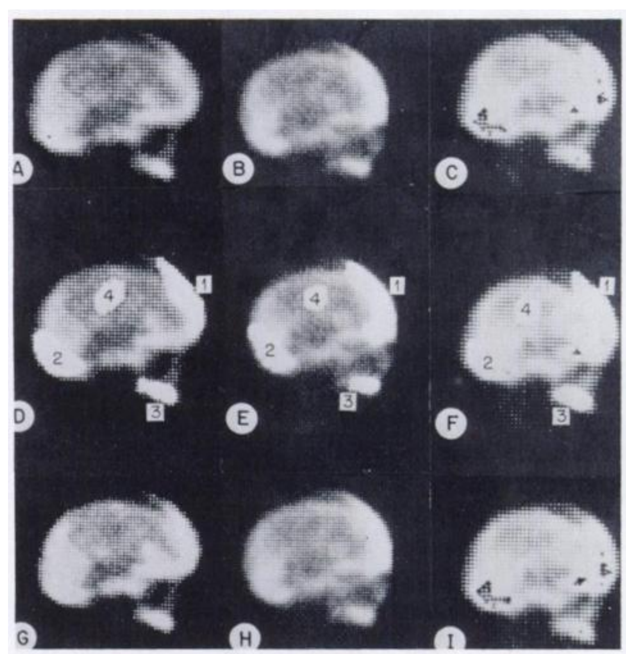

FIG. 2. Case 1, right lateral skull: (A) qualitative image, study #1; (B) qualitative image, study #2; (C) qualitative image, study #3; (D, E, and F) qualitative images for studies 1, 2, 3, with regions of interest indicated; (G) OUI, study #1; (H) OUI, study #2; and (I) OUI, study #3.

ferred to as "% uptake," keeping in mind that the relevant quantity is the change in uptake between studies.

The particular choice of background ROI in each frame will also influence the calculated uptakes and the appearance of the OUI. A background ROI for a frame is chosen in an area of soft tissue with a thickness typical of that part of the body. If the same set of background ROIs for a particular patient is always used, serial quantitative studies should be comparable. We believe our calculations adequately reflect these changes.

RESULTS

Two cases of Paget's disease studied by both qualitative and quantitative bone-imaging methods are submitted as examples of these techniques.

Case 1. A 64-year-old white man with known Paget's disease presented with right shoulder pain, hearing loss, elevated forehead temperature, and a systolic ejection murmur. His alkaline phosphatase at that time was 100 BU (normal = 6 BU). He was treated daily with 100 units of salmon calcitonin (*12,13*), given subcutaneously. At the time of his first quantitative bone scan, after 3 mo of therapy, he claimed he felt "fine." Most of his symptoms were relieved, and his alkaline phosphatase had fallen to 69 BU. Over the next year, however, he experienced dizziness and an increasing number of headaches, with a return of his murmur and a concomitant rise in his alkaline phosphatase to 100 BU.

TABLE 1. ROI UPTAKE DATA (CASE 1)*

Frame	ROI No.	After 3 mo therapy†	After 9 mo therapy†	After 15 mo therapy†
Lat. skull	1	1.27×10^{-2} 156	1.85×10^{-2} 268	2.27×10^{-2} 296
	2	1.58×10^{-2} 193	1.42×10^{-2} 207	2.94×10^{-2} 384
	3	1.22×10^{-2} 149	1.02×10^{-2} 148	1.96×10^{-2} 256
	4	8.67×10^{-3} 106	8.17×10^{-3} 118	1.38×10^{-2} 180
Ant. pelvis	1	3.64×10^{-3} 44.4	2.36×10^{-3} 34.3	4.47×10^{-3} 58.3
	2	6.50×10^{-3} 79.3	5.18×10^{-3} 75.2	8.62×10^{-3} 112
	3	8.08×10^{-3} 98.7	6.34×10^{-3} 92.1	1.45×10^{-2} 189
	4	4.32×10^{-3} 52.8	4.73×10^{-3} 68.6	9.72×10^{-3} 127
	5 (BKG)	2.73×10^{-4} 3.33	2.37×10^{-4} 3.44	4.41×10^{-4} 5.76

* Internal Standard = L Post Humerus.

† The first number in each entry is the % uptake/cell. The second is the $\frac{\text{\% uptake/cell (ROI)}}{\text{\% uptake/cell (Int Std)}}$.

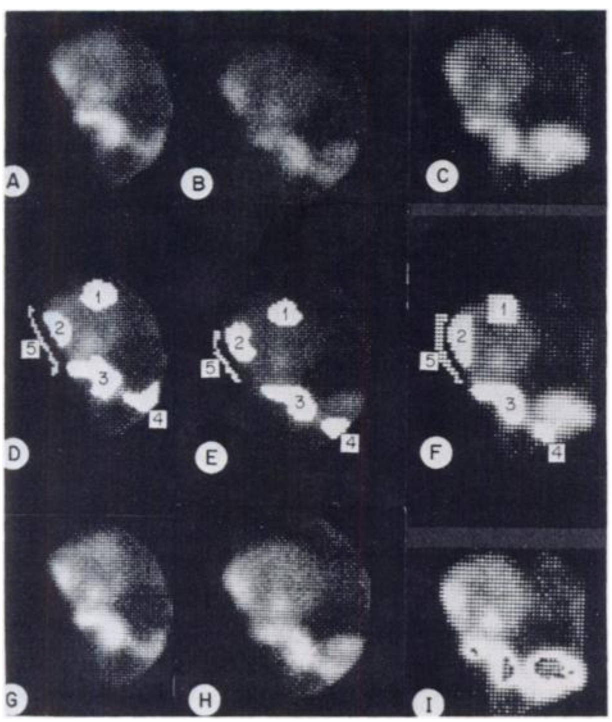

FIG. 3. Case 1, right anterior pelvis: (A) qualitative image, study #1; (B) qualitative image, study #2; (C) qualitative image, study #3; (D, E, and F) qualitative images for studies 1, 2, 3, with regions of interest indicated; (G) OUI, study #1; (H) OUI, study #2; and (I) OUI, study #3.

Figure 1 shows the anterior views from this patient's 1:5 rectilinear bone scan 3, 9, and 15 mo after the start of therapy. All three scans were performed on a dual probe scanner. Figure 2 shows various images of his skull taken at the times of the rectilinear scans; Figs. 2A, 2B, and 2C are unprocessed qualitative images; Figs. 2D, 2E, and 2F are the same images with ROIs included and labeled; and Figs. 2G, 2H, and 2I are OUIs. Figure 3 shows the right pelvic images at the times of the skull views in Fig. 2. The percentage uptakes per cell for the ROIs are given in Table 1.

Case 2. A 73-year-old white woman with known Paget's disease presented with pain in her right femur and pelvis. Her alkaline phosphatase was 22 BU. After 4 mo of treatment with 100 units daily of salmon calcitonin subcutaneously, her pain disappeared and her alkaline phosphatase fell to 12 BU. In addition, a warm area over her distal right tibia returned to normal temperature.

Figure 4 compares all the processed and unprocessed images of this patient's right femur before therapy and after 4 mo of therapy. Table 2 contains the percentage uptakes per cell for the ROIs.

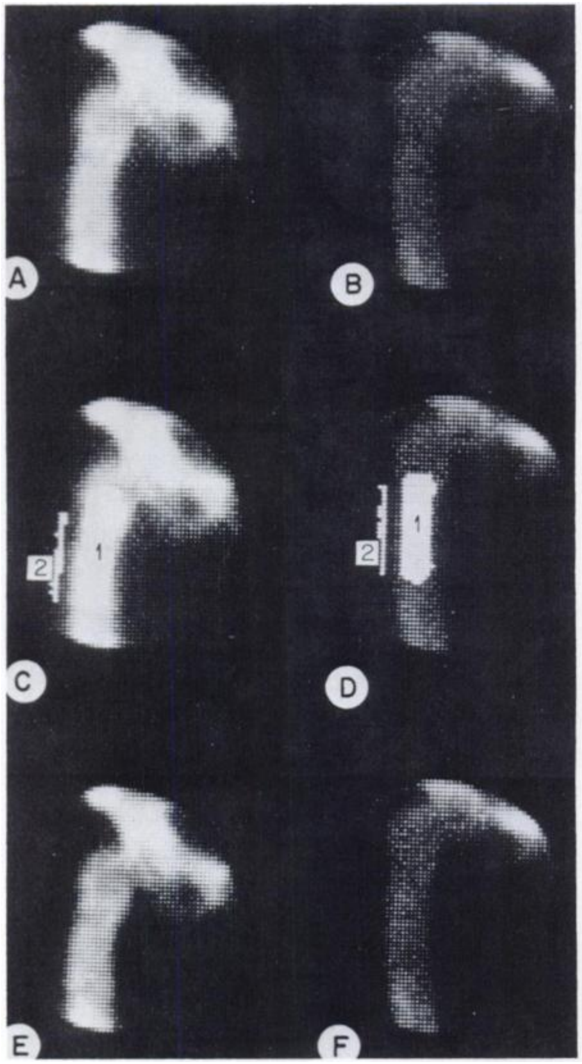

FIG. 4. Case 2, right anterior femur: (A) qualitative image, study #1; (B) qualitative image, study #2; (C and D) qualitative images for studies 1 and 2, with regions of interest indicated; (E) OUI, study #1; and (F) OUI, study #2.

DISCUSSION

Figures 1–4 and Tables 1 and 2 demonstrate how the bone-imaging techniques discussed in this paper represent the course of Paget's disease in both patients. It is significant that while both the qualitative and quantitative methods generally show change occurring in the same direction as the patient's symptoms and laboratory data, the extent of the apparent change differs with the method used. In the first patient, the progression of disease in his skull is obvious in Fig. 2, but the qualitative and quantitative techniques give different impressions of the rate of progress. The same is true of his pelvis. It is particularly important that this patient's rectilinear scans show relatively little change in his skull and that changes in his pelvis are exaggerated when compared with the OUIs. This is a good example of the influence that technical factors can have on the appearance of a scan. The second patient's femur shows decreased uptake on the post-therapy studies, but due to technical factors the qualitative images suggest a greater therapeutic effect than does the OUI study.

We believe that a quantitative method assesses the distribution of a radiopharmaceutical in the skeleton in a way that can be reliably compared in a series of studies of the same patient at different times. One must decide when to use ROIs, producing results such as those shown in Tables 1 and 2, and when to use OUIs.

An ROI study of a patient with many lesions may require a long processing time. Selecting exactly the same ROIs on a series of studies of such a patient can also pose problems. We therefore recommend the use of ROIs for following in detail a small number of diseased areas. On the other hand, OUIs can provide rapidly and accurately a more general description of the condition of a patient's skeleton. In some patients it is appropriate to use both techniques.

It is important to be aware of certain difficulties inherent in these quantitative methods. In anatomic regions such as the pelvis, there may be important differences in tissue absorption and background activity among various portions of the image. In ROI studies the use of the internal standard is based on the assumption that normal variations in the patient's metabolism alter radiopharmaceutical uptake uniformly throughout the skeleton. This may not be valid. In addition, the extent and, at times, the direction of change apparent in a ROI study depend on whether or not one uses an internal standard

TABLE 2. ROI UPTAKE DATA (CASE 2)*

Frame	ROI No.	Pre-therapy†	After 4 mo therapy†
R. Ant. Pelvis	1	3.55×10^{-3}	1.04×10^{-3}
		15.3	1.41
	2	1.45×10^{-2}	5.44×10^{-3}
		62.4	7.34
	3	1.20×10^{-3}	2.30×10^{-4}
	(BKG)	5.16	0.310
R. Ant. Femur	1	9.56×10^{-3}	3.29×10^{-3}
		41.0	4.44
	2	1.34×10^{-3}	4.86×10^{-4}
	(BKG)	5.76	0.656

* Internal Standard = L Ant. Iliac Crest.

† The first number in each entry is the % uptake/cell. The second is the $\frac{\text{\% uptake/cell (ROI)}}{\text{\% uptake/cell (Int Std)}}$.

(Tables 1 and 2). The explanation for this may be that a change in the uptake of abnormal bone leads to the opposite change in uptake by normal bone, and that pathologic areas of bone have an increased rate of uptake as well as a higher total uptake *(14,15)*. We are not yet prepared, however, to trust completely the use of internal standards, or even to recommend the most suitable areas of the skeleton for use as standards.

Regions of interest and OUIs provide the same type of information in different formats. (In fact, the sum of a group of cells on an OUI is equal to the uptake that would be found for those cells on a ROI study.) Regions of interest are best used to study a small number of areas while OUIs can provide information about the entire skeleton in view.

CONCLUSION

We have presented methods of quantitative bone scanning that reduce the uncertainties associated with qualitative imaging. Serial quantitative studies of two patients with Paget's disease compared favorably with the clinical and biochemical courses of their disease. One can present the quantitative information as either ROIs or OUIs, and each of these approaches has its own advantages.

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