A Complementary Method for the Detection of Osteoblastic Metastases on Digitized Radiographs

Angel González-Sistal, M.D., Ph.D.,¹ and Alicia Baltasar Sánchez, M.D.¹

Purpose: This study was conducted to evaluate the diagnostic usefulness of gray level parameters in order to distinguish healthy bone from osteoblastic metastases on digitized radiographs. **Materials and methods:** Skeletal radiographs of healthy bone ($n = 144$) and osteoblastic metastases ($n = 35$) were digitized using pixels 0.175 mm in size and 4,096 gray levels. We obtained an optimized healthy bone classification to compare with pathological bone: cortical, trabecular, and flat bone. The osteoblastic metastases (OM) were classified in nonflat and flat bone. These radiological images were analyzed by using a computerized method. The parameters (gray scale) calculated were: mean, standard deviation, and coefficient of variation (MGL, SDGL, and CVGL, respectively) based on gray level histogram analysis. Diagnostic utility was quantified by measurement of parameters on healthy and pathological bone, yielding quantification of area under the receiver operating characteristic (ROC) curve, AUC. **Results:** All three image parameters showed high and significant values of AUC when comparing healthy trabecular bone and nonflat bone OM, showing MGL the best discriminatory ability (0.97). As for flat bones, MGL showed no ability to distinguish between healthy and flat bone OM (0.50). This could be achieved by using SDGL or CVGL, with both showing a similar diagnostic ability (0.85 and 0.83, respectively). **Conclusion:** Our results show that the use of gray level parameters quantify healthy bone and osteoblastic metastases zones on digitized radiographs. This may be helpful as a complementary method for differential diagnosis. Moreover, our method will allow us to study the evolution of osteoblastic metastases under medical treatment.

KEY WORDS: Radiograph, osteoblastic metastases, computerized method, image analysis

INTRODUCTION

Metastatic cancer is the most common malignant bone tumor. Skeletal metastases are

classified, according to their radiologic appearance, as osteolytic, mixed, or osteoblastic. The distribution of skeletal metastases in adults is very similar to that of red marrow, which coincides with the trabecular bone.¹ Breast and prostate cancer account for approximately 80% of cases of bone blastic metastases.^{2,3} Osteoblastic metastases originating from tumors of prostate or breast may be involved in new bone formation given that they stimulate osteoblasts to produce collagen, osteocalcin, and alkaline phosphatases. Thus, the typical radiological imaging appears as an area of increased bone deposition. Diagnosis and classification of bone lesions are commonly made by a variety of imaging techniques, including radiographs and computerized tomography scans.

In an earlier work, an image processing and analysis method was introduced to characterize skeletal digitized radiographs. Preliminary results in healthy bone were promising.⁴ The characterization of healthy bone is important for the study,

¹From the Department of Physiological Sciences II, Faculty of Medicine, University of Barcelona, C/ Feixa Llarga s/n Pavelló de Govern, Lab. 41.57, 08907 Hospitalet de Llobregat, Barcelona, Spain.

Correspondence to: Angel González-Sistal, M.D., Ph.D., Department of Physiological Sciences II, Faculty of Medicine, University of Barcelona, C/ Feixa Llarga s/n Pavelló de Govern, Lab. 41.57, 08907 Hospitalet de Llobregat, Barcelona, Spain; tel: +34-93-4029088; fax: +34-93-4024268; e-mail: angelgonzalez@ub.edu

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Table 1. Number and anatomical distribution of ROIs for each healthy radiograph

Groups	Anatomical distribution of ROIs	Radiographs
CO (<i>n</i> = 240)	(<i>n</i> = 20) ^a : Humerus, Radius, Ulna,	Upper extremity (<i>n</i> = 20)
	Femur, Tibia and Fibula	Lower extremity (<i>n</i> = 20)
	(<i>n</i> = 24): Cervical, Thoracic, and	Vertebral column (<i>n</i> = 24)
TR (<i>n</i> = 240)	Lumbar vertebral column	Hand (<i>n</i> = 10)
	(<i>n</i> = 24): Carpus and Tarsus	Foot (<i>n</i> = 10)
	(<i>n</i> = 40): Skull, Pelvis	Skull (<i>n</i> = 20)
FB (<i>n</i> = 120)	(<i>n</i> = 10): Esternum, Ribs, Clavicle	Chest (<i>n</i> = 20)
	and Scapula	Pelvis (<i>n</i> = 20)

CO: cortical bone; TR: trabecular bone; FB: flat bone.

^a*n* for each bone indicated.

diagnosis, and treatment of bone diseases. Hence, by means of gray level parameters on digitized radiographs, we classified healthy bone according to histological and anatomical features. So, we reported an optimized healthy bone classification (trabecular, cortical, and flat bone).⁵

The aim of our study was twofold: to apply our method to digitized radiographs to obtain gray level parameters, and to assess the diagnostic usefulness of the gray level parameters to distinguish radiological images of healthy bone from osteoblastic metastases.

MATERIALS AND METHODS

Materials

The radiographs used in this article were obtained from the database of "Signal Analysis and Biomedical Images" group at University of Barcelona. We employed the images from two different classifications of the database: healthy bone and osteoblastic metastases. They were acquired at different radiology centers and were obtained in anterior-posterior projection.

A total of 144 healthy skeletal radiographs fulfilled the criteria for radiological normality and absence of bone

Table 2. Descriptive statistics for the characterization parameters: mean (MGL), standard deviation (SDGL), and coefficient of variation (CVGL) of gray level

Groups	N	Mean	SD	Minimum	Maximum
MGL					
CO	240	3,440	239.36	2,880	3,904
TR	240	2,752	223.04	2,176	3,184
FB	120	3,360	301.28	2,784	4,000
OM1	15	3,280	273.76	3,008	3,808
OM2	20	3,360	245.92	2,960	3,840
SDGL					
CO	240	94.94	35.68	18.14	267.03
TR	240	113.93	30.08	35.47	273.18
FB	120	113.23	27.04	54.84	232.40
OM1	15	75.77	20.48	33.08	119.57
OM2	20	82.65	15.68	44.70	130.56
CVGL					
CO	240	2.79	1.12	0.63	6.84
TR	240	4.14	1.25	1.63	8.58
FB	120	3.37	0.81	1.97	5.81
OM1	15	2.31	0.67	1.10	3.14
OM2	20	2.46	0.53	1.51	3.40

CO: cortical bone; TR: trabecular bone; FB: flat bone; OM1: nonflat bone osteoblastic metastases; OM2: flat bone osteoblastic metastases.

pathology. They were of 35 females and 89 males ranging in age from 18 to 85 years (mean, 47 years). Healthy bone cases were divided into three groups: cortical ($n = 240$), trabecular ($n = 240$), and flat ($n = 120$) bones (see Table 1). This classification was based on the characterization of healthy bone according to histological (cortical and trabecular) and anatomical (long, short, and flat bones) features. This allowed us to compare healthy with pathological bones.⁵

Thirty-five radiographs of osteoblastic metastases were selected in accordance with the following criteria: (1) official report specifying antecedent of prostate or breast cancer; (2) lesion confirmed by percutaneous biopsy (histologically, osteoblastic metastases were breast carcinoma in females and prostate carcinoma in males); (3) absence of multiple lesions on the radiograph; and (4) average size of the lesion on radiograph: 0.8–1.6 cm. They were obtained from 24 males and 11 females ranging in age from 56 to 70 years and from 41 to 57 years, respectively. They were classified into two groups: nonflat bone ($n = 15$) and flat bone ($n = 20$).

Methods

Acquisition

The radiographs were digitized by using a laser scanner (KFDR-S; Konica, Tokyo, Japan) with a 0.175-mm pixel size, a matrix size of $2,048 \times 2,048$ and 12-bit gray-scale levels.

Computerized Scheme

Our computerized method to characterize skeletal radiographs is summarized as follows: (1) selection of a region of interest (ROI), (2) filtering, (3) parameters output, and (4) data processing to distinguish between bone groups.

The images were processed using Image-Pro-Plus software. The algorithm was completely automated by Visual Basic language. The computational time required to produce a characterization image was about 15 s.

Regions of Interest

The cases were obtained from ROIs outlined by the first author using the mouse on each radiograph.^{6,7} ROIs of 100×25 pixels were selected to characterize the healthy bone. It was the minimum area that included only one kind of tissue (cortical, trabecular, or flat bone). An area of this size allowed

Fig 1. Descriptive boxplots comparing healthy bone groups with respect to the osteoblastic metastases. The median value and interquartile range are represented. (A) Mean gray level (MGL), (B) standard deviation gray level (SDGL), and (C) coefficient of variation gray level (CVGL). CO: cortical bone; TR: trabecular bone; FB: flat bone; OM1: nonflat bone osteoblastic metastases; OM2: flat bone osteoblastic metastases.

us to select cortical bones. ROIs of 40×50 pixels were selected on the basis of the studied tumors (0.8–1.6 cm), for osteoblastic metastases. The following consideration was borne in mind when selecting the ROIs from the radiographs. Each ROI had to have the same tissue for whole area (cortical, trabecular, flat bone, or osteoblastic metastases). ROIs containing several tissues were not employed given that the parameters used in the automated analysis perform averaging over the entire ROI area.

The number of ROIs taken from each healthy bone radiograph varied from one to six (Table 1 shows the number and anatomical distribution of ROIs for each healthy radiograph). We studied diaphysis, metaphysis, and epiphysis in cortex and medullary zones for extremities. Thus, it was possible to extract different six ROIs for each radiograph. Only one ROI from each osteoblastic metastases radiograph was used. The lesions were only located in the medullary space. The final set contained 600 ROIs from healthy bone and 35 ROIs from osteoblastic metastases. Data acquisition was used as a database to compare healthy bone with localized osteoblastic metastases.

Filtering

Radiographs differed essentially from other images in terms of dose limitation. For patient safety, the exposure dose is kept as low as possible. However, this impaired the quality of the image. Noise and blurring resulted in a reduced spatial resolution, whereas contrast and sharpness were inherent in the radiological image.⁸ An optimized filter was employed because parameters depended on gray level variations. The filtering technique consisted in applying a low-pass filter to the ROI. Filtering was mainly used to minimize the scattering of data.⁹

Parameters

The parameters derived from digitized radiographs were based on the gray level histogram analysis of ROI.

The mean gray level (MGL) is defined as the value given by the average of gray level of each ROI pixel, where summation is overall N pixels and x_i denotes the gray level at pixel i :

$$\text{MGL} = \frac{1}{N} \sum_{i=1}^N x_i \quad (1)$$

MGL provides 4,096 gray levels because we use images of 12-bit gray-scale (0–4,096, where 0 is equivalent to black and

4,096 to white). The diversity of cases used makes gray levels valuable within this range.

The standard deviation gray level (SDGL) of ROI pixel calculates the dispersion of gray values from the average (MGL). Dispersion is the difference between the actual and the average values. It is given by:

$$\text{SDGL} = \sqrt{\frac{1}{N-1} \sum_{i=1}^n (x_i - \text{MGL})^2} \quad (2)$$

SDGL can be expressed in relation to MGL as a coefficient of variation (in %) and is expressed as:

$$\text{CVGL} = \frac{\text{SDGL}}{\text{MGL}} \times 100 \quad (3)$$

These parameters are equivalent to information about anatomical, physiological, or malignant processes.

Statistical Methods

Standard descriptive summary statistics and boxplots were used to show overall trends in data. We routinely checked for normality of distributions using Q–Q plots. As distributions in the five groups considered were not severely skewed and variances were rather homogeneous, comparison among bone groups were implemented by using the one-way ANOVA test followed by the corresponding “post-hoc” tests (Tukey-HSD procedure) between pairs of groups. We performed receiver operating characteristic (ROC) analysis. Nonparametric estimation of areas under ROC curve (AUC)^{10,11} was carried out to assess the diagnostic ability of each parameter considered (MGL, SDGL, and CVGL) in healthy bone and osteoblastic metastases. Significance was considered to be reached at $p < 0.05$.

RESULTS

Table 2 and Figure 1 show the descriptive statistics for MGL, SDGL, and CVGL parameters for the different bone groups studied. MGL values were heterogeneous among groups ($p < 0.001$). When comparing SDGL and CVGL parameters, we found a significant difference in mean values ($p < 0.001$) although the results of both parameters were similar among groups.

Table 3. AUC values of the ROC curves for the three parameters considered and their corresponding significance

Groups	AUC		
	MGL	SDGL	CVGL
CO-OM1	0.67 ($p = 0.02$)	0.64 ($p = 0.07$)	0.61 ($p = 0.16$)
TR-OM1	0.97 ($p < 0.001$)	0.86 ($p < 0.001$)	0.93 ($p < 0.001$)
FB-OM2	0.50 ($p = 0.9$)	0.85 ($p < 0.001$)	0.83 ($p < 0.001$)

Null hypothesis tested (AUC = 0.5) corresponds to a null diagnostic value to differentiate between healthy and osteoblastic metastases groups.

CO: cortical bone; TR: trabecular bone; FB: flat bone; OM1: nonflat bone osteoblastic metastases; OM2: flat bone osteoblastic metastases. Mean (MGL), standard deviation (SDGL) and coefficient of variation (CVGL) of gray level. AUC: the area under the ROC curve.

Fig 2. Graphs shows ROC curves for the three parameters considered [mean (MGL), standard deviation (SDGL) and coefficient of variation of gray level (CVGL)]. (A) Cortical healthy bone vs. OM1; (B) trabecular healthy bone vs. OM1; and (C) flat healthy bone vs. OM2. OM1: nonflat bone osteoblastic metastases; OM2: flat bone osteoblastic metastases.

The ROC curves and the AUC values for all groups are shown in Table 3 and Figure 2. There were significant values of AUC when comparing image parameters for healthy trabecular/flat bone and osteoblastic metastases.

DISCUSSION

For MGL values, nonflat bone osteoblastic metastases had gray levels similar to those of healthy cortical bone ($p = 0.13$), but significantly higher levels ($p < 0.001$) than those of trabecular bone. Flat bone osteoblastic metastases had no gray levels that were significantly different from those of healthy flat bone ($p = 0.99$).¹²

As regards SDGL, flat bone osteoblastic metastases had gray levels lower than those of healthy flat bone ($p = 0.001$). Nonflat bone osteoblastic metastases had gray levels lower than those of healthy trabecular bone ($p < 0.001$), but these levels were not significantly different from those of healthy cortical bone ($p = 0.14$).

When discriminating between healthy cortical and nonflat bone osteoblastic metastases over 0.5 for MGL parameter, it was of little use to discriminate between them given that they showed a value below 0.8. Conversely, all three image parameters showed high and significant values for AUC when comparing healthy trabecular bone and nonflat bone osteoblastic metastases. MGL proved to have the best discriminatory ability (0.97).¹³ This is important for the differential diagnosis between the two groups because the distribution of skeletal metastases is closely related to the location of the trabecular bone. The new bone formation of blastic metastases is located on trabecular bone surfaces or is found in the marrow cavity as a primitive woven bone.

As for flat bones, MGL showed no ability to distinguish between healthy and flat bone osteoblastic metastases (0.50). This is probably because flat bone histologically is made up of the two cortical sheets, involving a small proportion of trabecular tissue (diploe: soft spongy material containing bone marrow). Moreover, it is almost equivalent to measuring cortical bone. Nevertheless, differentiation between healthy and pathological bones could be achieved by using either SDGL or CVGL, both of which showed a similar diagnostic ability (0.85 and 0.83, respectively).

There is no consensus on the best imaging method to diagnose osteoblastic metastases and to assess their response to treatment.¹⁴ In this study, we examined the usefulness of image parameters on digitized radiograph in the differentiation of healthy bone from osteoblastic metastases.

Consequently, our results demonstrate that gray level parameters quantify healthy bone and osteoblastic metastases zones on digitized radiographs. This can be helpful as a complementary method for differential diagnosis. Eighty percent of bone metastases are located in the axial skeleton (spine, ribs, skull, femur, and pelvis),¹⁵ which are mainly flat bones. Using SDGL and CVGL parameters, a diagnostic capacity of approximately 80% of blastic metastases located in flat bones was achieved. Moreover, with the rest of osteoblastic metastases, found in trabecular bone, all three parameters were applicable and had a good discriminating ability, especially MGL.

In conclusion, the ability to enhance accuracy between healthy and metastatic bones enabled us to complement the simple radiological exploration. The gray level parameters show a good discriminatory ability to distinguish between healthy trabecular/flat bones and osteoblastic metastases. The aim of developing a computer-aided diagnosis in the future is to improve diagnostic accuracy and interpretations of the radiologist by using the computer output as a guide. Furthermore, the method will be useful in studying the evolution of osteoblastic metastases under medical treatment.

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