

A software tool based on quantitative methods for the analysis of bone gammagrams

Software basado en metodos cuantitativos para analizar gamagramas oseos

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ABSTRACT

Objectives: We introduce a software tool to optimize the visualization of bone gammagrams, with the aim of differentiating (substantially) the pathologies from the radiotracer accumulation. The main objective of the mentioned software tool is to determine the presence of early-stage metastatic disease. The software contains routines capable of finding other types of anomalies and bone pathologies. **Materials and methods:** We analyzed a sample of 43 whole-body bone gammagrams, diagnosed with prostate cancer with ages ranging from 23 to 87 years (with a mean age of 55 years). We use several quantitative methods, such as histograms analysis, to analyze the gammagrams in gray tones. **Results:** Our proposed software is friendly, practical, and based on methods statistically robust, suitable for critical cases. We obtained optimal results in the search of degenerative changes, infections, or malign bone anomalies. **Conclusions:** The gray tone values in a bone gammagram depend on the bone health, with low order gray tones (around 20) corresponding to a healthy bone whereas values larger than 50 indicate the presence of bone disease. The gray tones distribution (besides their location) in the bone system is considered by the software for determining the bone disease type in the analyzed image.

Keywords: Bone gammagram. Bone metastatic disease. Digital image processing. Gray tones histogram.

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RESUMEN

Objetivos: Introducimos un software para optimizar la visualización de gammagramas óseos, con el objetivo de diferenciar las patologías de la acumulación de radiotrazadores. El objetivo principal de la herramienta informática mencionada es determinar la presencia de enfermedad metastásica en estadio temprano. El software contiene rutinas capaces de encontrar otro tipo de anomalías y patologías óseas. **Materiales y métodos:** Analizamos 43 gammagramas de cuerpo entero, diagnosticados de cáncer de próstata con edades comprendidas entre los 23 y los 87 años (con una edad media de 55 años). Utilizamos varios métodos cuantitativos, como el análisis de histogramas, para analizar los gammagramas en tonos grises. **Resultados:** Nuestro software es amigable, práctico y se basa en métodos estadísticamente robustos, adecuados para casos críticos. Obtuvimos resultados óptimos en la búsqueda de cambios degenerativos, infecciones o anomalías óseas malignas. **Conclusiones:** Los tonos gris en un gammagrama dependen de la salud, con tonos grises de orden bajo (alrededor de 20) correspondientes a un hueso sano, mientras que valores mayores a 50 indican la presencia de enfermedad ósea. La distribución de los tonos grises (además de su ubicación) en el sistema óseo es considerada por el software para determinar el tipo de enfermedad ósea en la imagen analizada.

Palabras clave: Gamagrama óseo. Metástasis ósea. Procesado digital de imágenes. Histograma de tonos de gris.

INTRODUCTION

The bone scintigraphy is the most widely-known technique used in the analysis of medical images to evaluate the spread of bone metastatic disease. In the case of breast cancer, the published data varies in terms of sensitivity and specificity between the reported ranges from 62 to 100% in sensitivity and 72 to 100% in specificity^{1,2}, even considering the influence of degenerative changes, infections, and fractures in producing false positives, dropping the efficiency of this type of diagnosis. In general, in a bone gammagram image, the gray tone values are low, causing the contrast to be inadequate for visual analysis, since the higher gray tones correspond to the bladder or a place where the radiotracer has

been injected, reaching in some cases the value 1024. This inconvenience and the osteoblastic activity imply a concentration caused by several causes, not necessarily a metastatic disease, hindering differentiating a metastatic disease from another anomaly or pathology.

In this work, we describe software based on quantitative methods to determine both benign and malign anomalies, with the aim of increasing the diagnosis accuracy. The software operation is based mainly on the analysis of gray tones in a region of interest (ROI) of a bone gammagram. The technique is based on the principle of the absence of radiotracer absorption in a ROI of a healthy bone system. Hence, every analyzed region

should have the same gray tone value (ideal gray tone) given that the gamma camera detects the presence of radiotracer in the bones, and if it is not detected, the all the ROI should display the same intensity. Every difference, despite its size regarding the ideal gray tone, would suggest the presence of an anomaly or pathology such as metastatic disease, osteoporosis, or a benign abnormal concentration.

MATERIALS AND METHODS

Our research on medical images based on nuclear medicine techniques started in 2015. We set as our goal analyzing the feasibility of increasing the diagnostic efficiency of bone gammagrams. To that aim, we started examining ten bone gammagrams from diseased patients diagnosed with prostate cancer³. In this work, we conclude that the gray tone value of healthy bones is low, between 20 and 30, with this value increasing only in the presence of an anomaly in the bone.

The 43 analyzed gammagrams were provided by the Department of Nuclear Medicine at Centro Médico Nacional “La Raza” where an analytic observational, retrospective, and analytic study was conducted from January 1 to December 31, 2015⁴. During this period, we conducted a statistical diagnostical study using a sample of 138 patients with prostate cancer with ages ranging from 47 to 85 years old (with a mean age of 68.5 years). The patients’ disease diagnoses were carried out using both the Gleason classification and bone gammagrams⁵. From the latter, we detected the presence and/or absence of bone metastatic disease from a visual inspection, performed for

comparative purposes in our proposal of the diagnostic software.

The bone gammagrams were obtained after administrating 25 mCi intravenous doses of the ^{99m}Tc-MDP radiotracer, and 2 l of water previous to the images capture. Two hours later, a radiopharmaceutical was administrated to the patients, and a whole-body scans were carried out with a dual-head MEDISO INTERVIEW XP Gamma camera VERSION 1.05014 with a LEHR collimator and a velocity of 12 cm/min in anterior and posterior projections. The bone gammagrams were subsequently visually analyzed by three specialists of the Nuclear Medicine department independently. The obtained diagnoses were used as a reference during our research in the software development and testing.

Out of the 138 analyzed bone gammagrams, 43 were whole-body scan type. The latter was set as the maximal sample of optimal gammagrams for our sample, considered to carry out our research based on the proposed software. To analyze the bone gammagrams and visualizing the ROI’s, the images were used in their original DICOM format, without being modified. We directly analyzed the “raw data” from the image file (“raw” DICOM images).

We performed a segmentation procedure using the software in the regions of interest (ROIs). We selected the region to be segmented in terms of the bone to be analyzed. For the sake of determining the presence of metastatic disease, we segment the bone system in five regions having a larger probability of metastatic disease occurrence, namely: skull, shoulders, thorax, scapula, and pelvis.

As we have previously mentioned, the software is capable of finding pathologies different than a metastatic disease, using two techniques: pixels switch-off and a comparison method. The pixels switch-off is indeed based on setting a black tone to the pixels where a substitution is performed, “switching-off” the pixel. This process is carried out by the software substituting by zero (“switching-off”) all the pixels with values lower or equal than a threshold value proposed by the user. Such a threshold can be arbitrarily selected, which posterior a previous practice using the software, we conclude it is lower or close to the ideal value mentioned in the introduction. The threshold value is increased by a unit until the bone or both bones in the case of the limbs are simultaneously switched-off if they are healthy. If the bone displays a completely black appearance in contrast to the other one, the one with values different from zero will be considered to have an anomaly.

The search for bone anomalies or pathologies different than a metastatic disease is carried out by the software by segmenting the region of the bone where the patient reports pain or discomfort is located. In the case of upper or lower limbs, the software will perform the segmentation of the region containing both left and right limbs. In the case of an arbitrary bone, it suffices to perform the segmentation of the region containing the whole bone due to the quasi-symmetric property of the bone system, with the aim of applying a comparative method based on the comparison of the pixels substitution in both sides, left and right. To this aim, the images are displayed following this criterion: a pair of bones is chosen, for example, the femur, and the software proceeds to switch-off the image pixels, setting

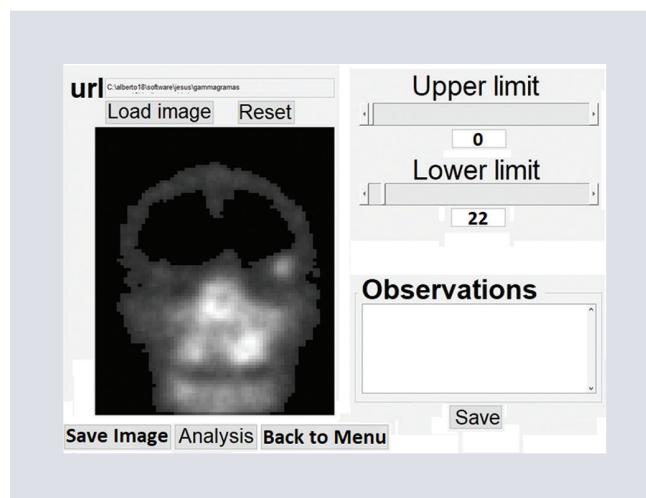


FIGURE 1. Visual interface to substitute by zero the pixels in the ROI.

to zero the image pixels below the given threshold value. Such a value is subsequently increased by a unit until both bones are almost simultaneously switched-off in the case of healthy bones. If one bone is switched-off before its counterpart, it is suggesting the presence of an anomaly (Fig. 1).

An advantage of the simultaneous use of these two methods is given by the possibility to find the geometry and location of the ongoing bone anomaly. In figure 1, we show the application of the method to perform the substitution of the skull pixels values. Using the right-most top bar, the high gray tone values are replaced by zeros, and the bottom bar allows us to replace the low gray tones by zero. The value 22 observed at the right side, indicates values lower or equal to 22, previously substituted by zeros, and seen in the ROI in black inside and outside the skull. In the left panel of figure 2, we show three analyzed ROIs. In the right panel of the figure 2, we observe the anomalies found using both methods simultaneously, namely, pixel substitution and comparison of the skull region and

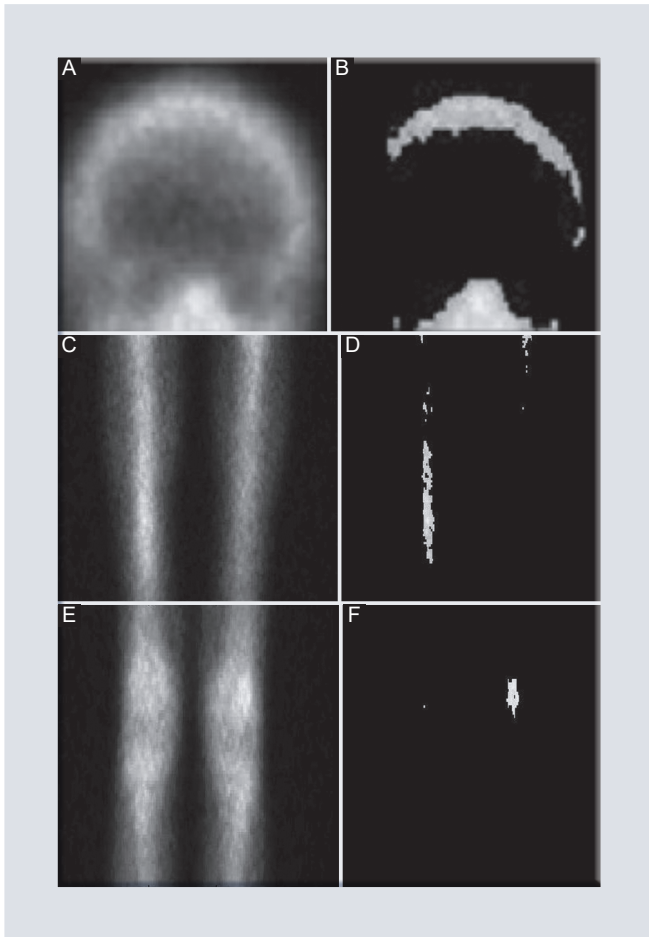


FIGURE 2. Show three bone benign anomalies obtained by applying substitution and comparison methods in three regions. **A-B:** for the skull. **C-F:** for the lower limbs.

two lower limbs, displaying the position and extent of the bone anomalies obtained by applying the procedure in figure 1.

Regarding figure 2B, we found in the literature a method giving identical results to the method reported by us. We obtained results by applying such a method, using two gammagrams with different radioactive tracers for the same patient. The obtained gammagrams were subsequently subtracted from each other⁶. This method represents a risk for the patient's health as well as being more time-consuming and expensive. We use the

knowledge of the observed image gray tones to determine whether the anomaly is benign or malignant, as well as to determine the stage of metastatic disease, as we will see in the following.

RESULTS

We proceeded to optimize the software devoted to analyzing bone gammagrams to search for metastatic disease with the aim of applying it in the detection and diagnosis of early-stage metastatic disease.

Detection of ongoing metastatic disease

We used a sample of 43 gammagrams, and we analyzed each one in five ROIs. We performed a statistical process to create the gray tone intervals that gave place to the interval tables used to visualize the ROIs in color and subsequently determine the stage of the bone metastatic disease, where each ROI (skull, shoulder, thorax, scapula, and pelvis) has a high probability of developing bone metastatic disease. Subsequently, we computed the mean and standard deviation of the minimum and maximum values found in each ROI of the sample, separating healthy and metastatic disease cases accordingly. From the mean and standard deviation values, we built the gray tone intervals of the sample constituted by 43 skulls. This procedure was repeated with the four remaining ROIs. To separate healthy bones from those with metastatic disease, we used the diagnoses provided by three specialists at "Centro Médico la Raza" at IMSS, that

performed a visual inspection of the bone gammagrams.

The proposed software uses the minimum and maximum gray tones of the five ROIs in each gammagram to determine the stage of the metastatic disease, considering that a bone without osteoblastic activity will not absorb the radiotracer, and hence the corresponding gray tone should be zero. However, in the bones natural processes, regeneration is constantly occurring causing radiotracer absorption leading to non-zero gray tone values. This depends critically on the patient's age, race, gender, used radiopharmaceutical type, scan velocity, etc. In the case of a single patient, the absorption of the radiotracer, as well as the minimum and maximum gray tones of each ROI will be unique. For a given sample of patients (as for different ROIs) such values will form an interval since every patient's bone will not display the same gray tones. We performed the segmentation of each ROI intending to obtain the different gray tones intervals, considered for the assignation of the seven colors (false color), assigning different colors for each region and hence differentiating healthy cases from infiltrated ones for ROI, easing the diagnostic⁷.

For illustration purposes, we show the analysis of a subsample of ten skulls free from metastatic disease and healthy (considering any other pathology) to determine the gray tone intervals as shown in table 1. The minimum value corresponds to the lowest value found in each skull, the maximum value 1 corresponds to the gray tone value found by switching-off a given skull region set as a reference, the maximum value 2 corresponds to the highest gray tone found in each skull.

Table 1. Reported values for our sample of ten healthy skulls

ROI ID	Minimum value	Maximum value 1	Maximum value 2
1	9	30	34
2	13	41	44
3	15	56	60
4	17	32	39
5	15	47	56
6	12	43	43
7	10	38	38
8	15	51	54
9	13	38	41
10	16	48	55
Mean value	13.5	42.4	46.4
Standard deviation	2.2	9.0	11.0

We consider the process to determine the gray tones as a measurement and the standard deviation (st) as the mean value uncertainty (value \pm st). We generated ten intervals with the data shown in table 1 as follows: The first interval was created to color with only one color the image background. Such value is obtained by subtracting the mean value in the second column of the table to the corresponding standard deviation finally, subtracting a unity to color only the background. The second interval is computed considering the mean value plus its st. Hence, the latter interval ranges from 11 to 16. Such interval is considered as \pm st of a measurement. Thus, any healthy skull will have its lowest gray tone between 11 and 16.

We assign the color to each shown interval using table 2, and we display such values in table 3. We used table 1 to apply color to the

Table 2. Built intervals with the values shown in table 1

Interval number	Start	End
1	0	10
2	11	16
3	17	32
4	33	57
5	58	124
6	125	191
7	192	255

Table 3. Assigned color intervals in terms of the minimum values of the histogram

Interval Number	Minimum Value	Maximum Value	Assigned color
1	0	min	Blue
2	min + 1	max	Royal Blue
3	max + 1	max + 11	Green-Blue
4	max + 12	max + 27	Green
5	max + 28	255	Yellow-Green

skull in figure 3A and using similar tables for the non-healthy and infiltrated skulls in figures 3B-C.

A remarkable advantage of the proposed technique is that it requires only one “calibration” to visualize similar ROIs with ongoing metastatic disease in colors (false color). The software uses five tables, each one for a different ROI, from which an arbitrary bone gammagram can be analyzed. A disadvantage is given by the software requirement of a large number of gammagrams to ensure reliable color assignation for calibrating the routines in our proposal. For our work purposes, we calibrated the software using only

43 gammagrams, with only ten corresponding to healthy skulls. Hence, larger gammagram samples are required to improve the software.

Search of early-stage metastatic disease

The technique described in this section is intended to visualize ROIs with early-stage metastatic disease in colors to allow the specialist to determine if the observed color is different from the corresponding of a healthy bone and hence diagnose the stage of the metastatic disease. Subsequently, the specialist will decide whether to ask for additional studies or not or if the diagnosis can be inferred and thus take the pertinent actions, given the functionality of the software to assist the specialist in making a decision rather than performing a diagnostic (Fig. 4).

After a thorough analysis of the stressed arguments in the previous sections, we developed a method to help to visualize the early-stage metastatic disease in bone gammagrams, contributing to this problem solution. Our proposal is based on the gray tones histogram observation of the analyzed ROI. An advantage of this modality is that only one gammagram is required instead of a large sample. A segmentation procedure is performed to the bone gammagram in six regions: skull, shoulders, thorax, vertebral spine, scapula, and pelvis, since each region displays different histograms and it is not possible to group all the regions for analysis. In these six ROIs healthy bones have bimodal gray tones histograms, showing two minima (Fig. 4B). Such a feature eases the selection of

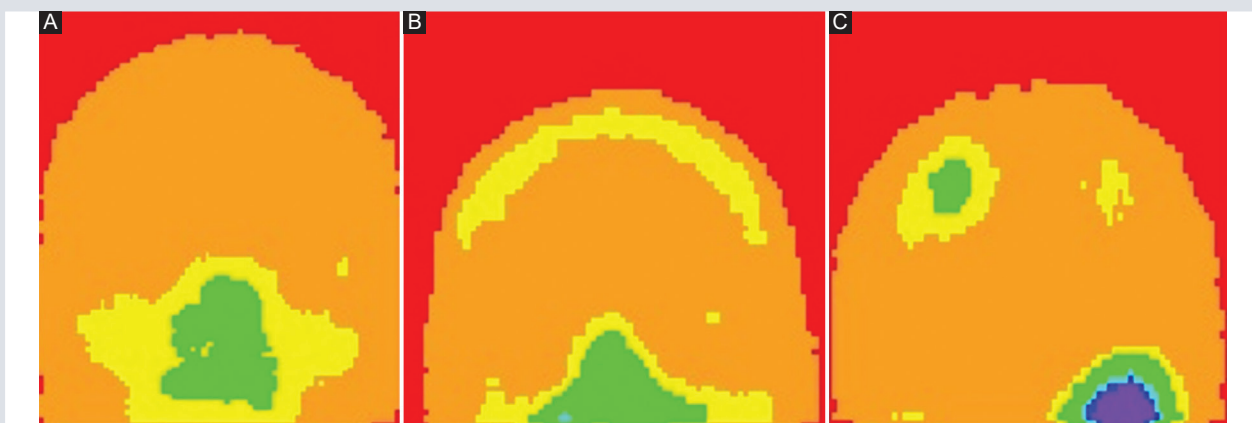


FIGURE 3. Three different skulls illustrating the application of false color to optimize the visualization of anomalies. **A:** show ideal case. **B:** show a non-ideal case. **C:** show an infiltrated case.

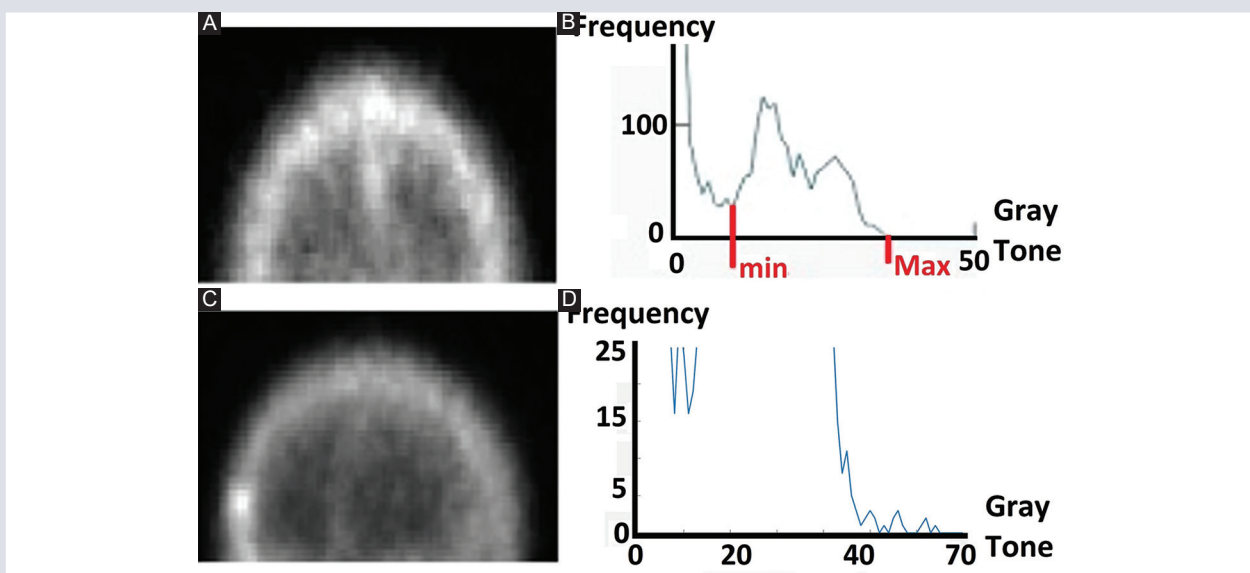


FIGURE 4. **A-C:** show skulls in free of metastatic disease, and with early-stage metastatic disease. **B-D:** show their corresponding histograms (right panels).

only two intervals to visualize a ROI free from metastatic disease. Hence, in this particular case, two colors are sufficient to visualize the ROI: from 0 to min and from min + 1 to max. However, considering that a given ROI can have metastatic disease, it is necessary to

add color indicating early-stage metastatic disease. The minimum gray shown in Fig. 4B by a red line in the left, separates the dark background from the rest of the image. In the case of a healthy skull, the maximum image gray tone will be lower than 50, and the right

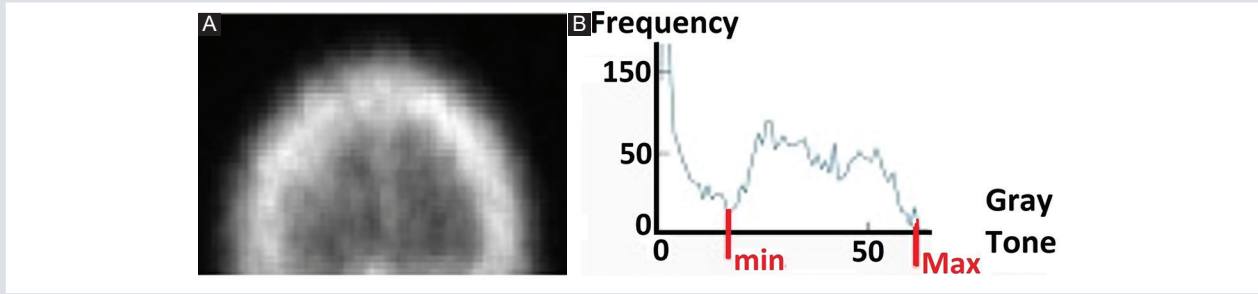


FIGURE 5. **A:** a skull with a degenerative disease. **B:** the corresponding histogram. We draw special attention to the distance increase between both minima and their shift to the right.

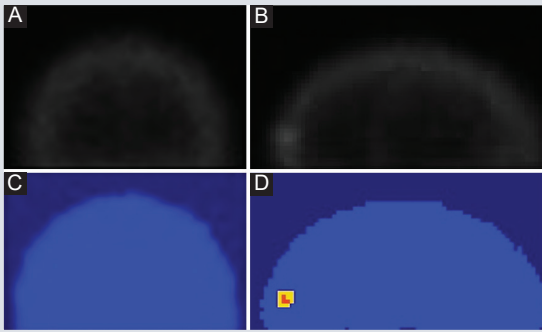


FIGURE 6. **A-C:** two skulls: a healthy one and with metastatic disease. **B-D:** before and after applying false colors.

end of the histogram will rapidly drop to zero. In this particular case, three intervals are sufficient. Hence, three colors are enough and thus three colors for visualizing the ROI: from 0 to min, from min + 1 to max, and from max to max + 1 and beyond (Fig. 5).

To add color to the ROI it suffices to select only the two observed minima in the histograms, from which tables with three intervals are built. Occasionally, it is possible for a bone free from metastatic disease to have a degenerative disease, causing the distance of the two minima to be increased, as well as their

values (Fig. 5B). To observe these anomalies along with the early-stage metastatic disease, it is possible to add two additional intervals between both minima, ensuring the interval table to increase. We do not show the argument in this work.

At this point, the most interesting cases regarding the analysis performed with our proposed software are those corresponding to early-stage metastatic disease (considering the histogram in figure 6), taking into account the gray tones indicating the presence of the disease, as we show as local maxima in the plot as low-amplitude curls extending along the x-axis. To determine the extent of ongoing metastatic disease, it is highly-recommended to use an additional color to visualize the ROI. Finally, we show the table for color assignment in table 2. We decided to increase 10 gray tones after the max value for the early-stage metastatic disease, and for the late-stage metastatic disease, we assigned a value of 15. It is also possible to select these values arbitrarily. However, in the early-stage metastatic disease case, the min value cannot be lower than 3, and the maximum larger than

10. Ideally, a $\text{max} + 1$ value should suffice to determine the presence of early-stage metastatic disease, considering the stochastic processes taking place during the emission and detection of the energy involved in the osteoblastic activity due to the action of the radio-tracer. The fifth interval is added in case the ROI has pixels with gray tone values larger than $\text{max} + 27$.

The values assignments for increase (10 and 15) could be either arbitrarily chosen or given in terms of the specialists' so-called metastatic disease stages, using the colors to indicate the metastatic disease stage.

We bear in mind that the table is created for each ROI in the gammagram and every single patient. Hence, we display the histogram in the first place. The color assignments using false color are performed based on the intervals in the tables for the ROIs.

One practical feature of the software is the dynamical creation of up to ten intervals considering the colors selected by the user. In Fig. 6, we show the result in color, for two skulls, a healthy and one with an ongoing metastatic disease in 6.a. and 6.c, respectively. If we observe Fig. 6.d only using yellow, we can conclude we are detecting an early-stage metastatic disease since this color corresponds to the interval $\text{max} + 10$. Provided that we are also using orange, we state we are detecting an ongoing metastatic disease given that this color corresponds to the interval $(\text{max} + 11) + (\text{max} + 25)$. In particular, from this figure 6, we can infer a relationship between the added colors and the ability to determine the stage of metastatic disease, with a larger list of colors

easing the determination of the metastatic disease stage.

DISCUSSION

We have laid out the minimum tools required for a software tool to be efficient for the analysis of bone gammagrams. We consider that both the shape and the distribution of the switched-on pixels, as well as the minimum and maximum gray tone values, are crucial for determining the type of bone pathology (benign or malignant) suffered by a patient. The software can only complete such a task successfully if it has the features for performing the analysis of the gray tone of the ROI along with functionalities to visualize the histogram, supported by the addition of false-color for each ROI to ease the pathologies visualization.

The pixels switch-off method, along with the comparison between pairs of gammagrams, are efficient in finding the differences in up to one or two gray tones, allowing to determine the type of disease different than a metastatic disease, thus increasing the efficiency of the bone gammagram. In a forthcoming paper, we will delve into the interesting issue of the increase of the minimum values of a healthy bone starting to suffer an early-stage metastatic disease³ since such values should remain constant in principle. The latter could be explained by the influence of the metastatic disease on the bone, either affecting a larger zone or increasing due to an inflammatory process in the bone. To answer such questions, we will require an additional technique to analyze the bone system from nuclear medicine or another field.

For a person familiar with the described methods (MD or any other researcher), it is possible to detect an early-stage metastatic disease from the observation of the gray tones histogram of a gammagram, thus concluding if the bone is free from a metastatic disease without inspecting the image. Such expertise, however, can only be obtained with the time and proper training undertaken by the personnel devoted to visually analyzed gammagrams.

We also point out that the process for determining the sensitivity and specificity of the software is still pending since we are not an oncologic center and, we do not have a large number of gammagrams available for analysis. This step has not been completed yet.

We implemented the software in the Matlab[®], which requires a paid license. However, we are currently developing it in free software platforms such as Java and Python, to ensure also the availability of GUI or executable file soon to be used without restrictions or paid licenses. All the health institutions interested in a trial version or a copy of the software can contact the principal author of this work to obtain a free copy through a technology transfer contract.

CONCLUSIONS

We developed a software tool to analyze bone gammagrams based on quantitative methods. As we have previously shown, the software is capable of finding benign degenerative diseases involving radiotracer absorption, and hence an increase of the image

pixels gray tones. In this case, the methods of pixels substitution (pixels switch-off) and histogram comparison have proven to be efficient.

We found that the most efficient method to determine the stage of a metastatic disease is the visualization of the region of interest using colors. To apply such a technique, we proposed seven gray tones intervals for which different false colors are assigned for each interval, including the background, for the position, distribution, and stage of metastatic disease. In this case, the intervals were estimated from a statistical process, performed with the gray tones of five different ROIs, for each bone gammagram in the sample of 43.

The most highly recommended technique for determining the tones corresponding to early-stage metastatic disease is the inspection of the image gray tone histogram. It can be applied in the observation of a particular ROI (a subregion, e.g., a bone), carrying out the visualization in colors using the two observed histogram minima. Three colors would suffice to perform the visualization of early-stage metastatic disease; however, it is recommended to use at least for colors and less than seven if the ongoing metastatic disease is intended to be observed.

Our proposed software is not automatic but manual and slightly more time consuming than other tools. However, it allows us to detect several diseases, anomalies, or pathologies from a single gammagram. Despite having a slightly larger execution time, the software is fast enough to be recommended for use in medical centers with large patients

flux, requiring personnel with experience in the gammagram analysis.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest with this work.

FUNDING

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ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the

regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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