Designing an analysis system for imaging process from bone scintigraphy as a potential predictor for validation of bone metastases

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Abstract: Cancer is a disease that leading cause of death worldwide. In 2012, there were 8.2 million deaths caused by cancer. Cancer suffered by patients can metastasize to other body parts, such as the lungs, liver, brain, and bones. The risk of bone metastases becomes higher after cancer has spread to other body tissues, so it is necessary to do more specific bone examinations. Bone scintigraphy is one of the applications from nuclear medicine that utilizes ^{99m}Tc radioactive material as a radio-pharmaceutical for bone scanning examinations. Bone scintigraphy is done to determine the presence of metastases in the bone caused by cancer. This bone scan is an image capture method with high sensitivity but has the disadvantage of not clearly distinguishing the presence of hotspots that appear due to metastases, trauma, or other abnormalities in the bones. This research aims to create an analysis system design based on image processing scripts using MATLAB. Medical physicists and nuclear medicine technicians can later use this system to conduct quantitative analysis as a reliable predictor system that validates visual analysis of hotspots suspected of being metastasis of cancer. Based on the result, prediction of the presence of bone metastasis by quantitative analysis using digital image processing techniques can be made. With a significance level of 5%, prediction results from the analysis system design resemble patient's medical records data with (85.67% ± 12.71%) accuracy.

***Keywords**: bone scan, cancer, metastases, nuclear medicine, technetium*

1. Introduction

Cancer is one of the leading causes of death worldwide. In 2012, cancer was the cause of death for an estimated 8.2 million people. Based on GLOBOCAN data, the International Agency for Research on Cancer (IARC), it is known that in 2012 there were 14,067,894 new cases of cancer and 8,201,575 deaths from cancer worldwide. The most significant causes of cancer deaths each year include lung, liver, stomach, colorectal, and breast cancer.[1] Cancer is a condition where there is uncontrolled or abnormal cell growth. As it grows and develops, cancer cells could also spread (metastasize) to other parts of the body or other healthy tissues far from their original location. This spread occurs through blood vessels and lymph vessels. It causes new cancers in different areas of the body.[2] Cancer cells can come out of a malignant tumor and then spreads to other parts of the body through the bloodstream and lymph flow. Bone is one of the body parts that are the most frequent metastasis site,[3] so it is often necessary to do a more specific examination of the bone. Usually, we examine it using the bone scanning method with bone scintigraphy.

Bone scintigraphy, or commonly referred to as bone scan, is a nuclear imaging technique in which a small amount of radioactive material is injected into the vein to highlight areas of bone damage or disease. The injected compound,

called a tracer, is taken up in cells and tissues undergoing repair. A bone scan is a relatively safe procedure and is useful for diagnosing several bone conditions, including fractures, infections, and cancer.[4] Bone scan examination results are in the form of images or images with dots in the way of hotspots that can indicate abnormalities in the bone. Image is a representation, identically, or imitation of an object. We divide images into 2 types, namely analog images, and digital images. Analog image is a continuous image, such as images found on television monitors, X-ray photos, CT scans, etc. Meanwhile, digital images are images that can be processed by a computer. A matrix with m columns and n rows could represent digital images, where the intersection of the columns and rows is a pixel, which is the fundamental element of an image.[5]

Image processing is the means of processing pixels in a digital image for a specific purpose. In the acquisition process, we transform the image to be resolved into a numeric representation, which is then processed digitally by a computer. Image processing itself can be grouped into 2 types: improving image quality as needed and processing the image's information. Clinically, to determine whether a hotspot is metastatic or not can be done visually or qualitatively by image analysis by an expert (specialist doctor). However, the visual inspection often gives the wrong result. Therefore, it is necessary to have a strong predictor in the quantitative analysis used as a validation system.

This study aims to design an image processing script-based analysis system that can help and facilitate medical physicists or nuclear medicine clinicians to validate the presence of hotspots on images caused by metastases cancer or not. Image data taken are from cases of breast cancer, lung cancer, and prostate cancer. This algorithm can be used to detect the presence of metastases with an accuracy of 80%.

2. Materials and methods

The implementation of this research was carried out in four stages, namely literature study, preparation for data collection, patient data collection, and script design and analysis. A literature study is carried out to collect important references and information that support research. The references used are taken from online and offline sources. It provides information about image processing with MATLAB, an examination by bone scintigraphy, bone scan index, breast cancer cases, prostate cancer, lung cancer, and how bone metastasis caused by cancer.

The next stage is the preparation for data collection. We prepare patient data collection at dr. Kariadi Hospital Hospital, Semarang, makes ethical clearance and applies for research permits to the Education and Research department at dr. Kariadi Hospital. After that, we collected the secondary data of patients with breast cancer, lung cancer, and prostate cancer at dr. Kariadi Hospital, Semarang. The amount of data used in this design is 30 samples, with details of 11 samples of patients with breast cancer cases, 9 samples of lung cancer patients, and 10 samples of prostate cancer patients. The data that we have are images from examination results with a bone scan with DICOM file and data archives of patient medical records in .docx documents.

The last stage is the analysis system design. This stage was carried out after obtaining secondary data from dr. Kariadi Hospital. The design was carried out using MATLAB R2017b software. Then sample testing is carried out after the plan of the image processing script-based analysis system program has been successfully created. Validation of the suitability of image reading results from the system is carried out by confirming the data archives that we have taken from the Radiology Installation of dr. Kariadi Hospital, Semarang.

There are 2 types of criteria for determining the presence of metastases used in this study, namely the inclusion criteria and the exclusion criteria. The inclusion criteria are metastatic criteria specified before we carried out the image processing process with our MATLAB program, which includes: breast cancer, prostate cancer, and lung cancer patient from dr. Kariadi Hospital on examination March - June 2019; hotspots that are positive for metastasis is generally in an asymmetrical location (not in the joint area). Whereas if hotspots are found in the joint area, it is necessary to re-validate by observing the density of hotspots in the figure; metastases are often located in long bones or bones close to where the primary cancer is, and metastases that appear are osteoblastic.[6]

Meanwhile, the exclusion criteria are metastatic criteria used after the bone scan results were processed using our MATLAB program. In general, the program produced in this study will mark all selected objects from the results of image processing using morphological techniques without size limitations, which are marked with a number label. The program will read objects that have size between 50 to 3000 pixels and identify it as a hotspot marked with ROI. However, if the hotspots do not meet the inclusion criteria, it is necessary to re-validate them by reviewing the density of hotspots, which is marked with ROI. Objects with number labels that meet the inclusion criteria should be checked

regarding the density of the object and using a 9-segment index to validate the determination of the presence of bone metastases. The smallest object size read by the analysis system designed in this study is 13 pixels.

The method used in designing this program is to combine four basic digital image processing techniques, namely image segmentation techniques, thresholding techniques, morphological techniques, cropping techniques, and marking of the desired object. **The segmentation technique** is partitioning the image into several areas that aim to separate parts of it from the background in the image to make it easier to analyze the object.[7] **The image segmentation** process is based on the degree of gray in the image, such as converting a color image that has a matrix value of r, g, and b respectively into a grayscale image with matrix values, which is the average value of the r, g, and b values.[8]

The thresholding technique is used to separate the object from the background based on the difference in the image's intensity level. The dark side's location will have an intensity value of 0, and on the bright side of it will have an intensity value of 1. This technique is also known as the grayscale image conversion technique to binary.[9] **The morphological technique** can be defined as a technique of separating objects in an image based on the object's structure and shape.[10] In designing this program, **the cropping technique** is carried out separately and aims to obtain the boundary value used in determining the index. The marking is done in 2 ways, namely using the Region of Interest (ROI) and numbering. Objects marked with ROI are objects whose pixel size meets the range of values in the exclusion criteria. In contrast, objects labeled with numbers are all objects produced in image processing using morphological techniques.

3. Results and discussion

The 9-segment index is determined by dividing the body frame into the 9 parts, namely two upper limb bone segments, two lower limb bone segments, two rib segments, one spinal segment, one pelvic area segment, and one bone segment in the head area. Segment division is done by cropping the image based on image data of patients with a posture that is assumed to be the most proportional. The range value on the index is obtained by calibrating the measurements for each segment against 30 samples of patient data.

We used the size of the digital image basic structure as the basis of our quantitative analysis. The system can recognize the object as metastasis by selecting the object size based on a predetermined range value. Another parameter that is the basis for determining metastases in this study is the index value of 9 segments. The index can be seen in Table 1. In addition, there is a density variable obtained from the intensity value of each image pixel produced in the segmentation technique. The determination of the high and low density is determined based on the degree of the grey level of the image pixel intensity. In this study, high-density values ranged from 170 to 255, and low-density values ranged from 1 to 169.

Table 1. Calibration result of index data for each segment.

No.		*Hot-spots Location*	*Hot-spots Area (pixel)*	*Symmetric Location*		*Density*		*Prediction*	
				Yes	*No*	*High*	*Low*	M	N
1		Upper limb bone (right)							
	-	*Humerus*	17<Area<50	-	-	1	-	M	-
	-	Shoulder-Arm Joint	50<Area<500	1	1	1	1	M	N
	-	*Ulna*	17<Area<50	-	-	1	-	M	-
	-	*Radius*	17<Area<50	-	-	1	-	M	-
	-	*Humerus-Radius* Joint	50<Area<500	1	1	1	1	M	N
	-	*Carpal*	50<Area<500	1	1	1	1	M	N
	-	*Metacarpal*	17<Area<50	-	-	1	-	M	-
	-	*Phalanges*	17<Area<50	-	-	1	-	M	-
2		Upper limb bone (left)							
	-	*Humerus*	17<Area<50	-	-	1	-	M	-
	-	Shoulder-Arm Joint	50<Area<500	1	1	1	1	M	N
	-	*Ulna*	17<Area<50	-	-	1	-	M	-
	-	*Radius*	17<Area<50	-	-	1	-	M	-
	-	*Humerus-Radius* Joint	50<Area<500	1	1	1	1	M	N
	-	*Carpal*	50<Area<500	1	1	1	1	M	N
	-	*Metacarpal*	17<Area<50	-	-	1	-	M	-
	-	*Phalanges*	17<Area<50	-	-	1	-	M	-
3		Lower limb bone (right)							
	-	*Femur*	20<Area<50	-	-	1	-	M	-
	-	*Patella*	12<Area<50	1	1	1	1	M	N
	-	*Patella* Joint	50<Area<3000	1	1	1	1	M	N
	-	*Tibia*	20<Area<50	-	-	-	1	-	N
	-	*Fibula*	20<Area<50	-	-	-	1	-	N
	-	*Tarsal*	50<Area<500	1	1	1	1	M	N
	-	*Metatarsal*	17<Area<50	-	-	1	-	M	-
	-	*Phalanges*	17<Area<50	-	-	1	-	M	-

Table 2. Calibration result of index data for each segment (cont.).

No.		*Hot-spots Location*	*Hot-spots Area (pixel)*	*Symmetric Location*		*Density*		*Prediction*	
				Yes	*No*	*High*	*Low*	M	N
4		Lower limb bone (left)							
	-	*Femur*	20<Area<50	-	-	1	-	M	-
	-	*Patella*	12<Area<50	1	1	1	1	M	N
	-	*Patella* Joint	50<Area<3000	1	1	1	1	M	N
	-	*Tibia*	20<Area<50	-	-	-	1	-	N
	-	*Fibula*	20<Area<50	-	-	-	1	-	N
	-	*Tarsal*	50<Area<500	1	1	1	1	M	N
	-	*Metatarsal*	17<Area<50	-	-	1	-	M	-
	-	*Phalanges*	17<Area<50	-	-	1	-	M	-
5		Ribs (right)							
	-	*Costae*	20<Area<50	-	-	1	-	M	-
6		Ribs (left)							
	-	*Costae*	20<Area<50	-	-	1	-	M	-
7		Spine							
	-	*Vertebrae* Cervix	50<Area<3000	-	-	1	1	M	N
	-	*Vertebrae* Thorax	50<Area<3000	-	-	1	1	M	N
	-	*Vertebrae Lumbal*	50<Area<3000	-	-	1	1	M	N
8		The bones in the hips							
	-	*Pelvis*	50<Area<3000	-	-	1	1	M	N
	-	*Ilium*	50<Area<3000	-	-	1	1	M	N
	-	*Iscium*	50<Area<3000	-	-	1	1	M	N
9		Bone in the head area							
	-	*Frontal*	13<Area<100	-	-	1	-	M	-
	-	*Parietal*	13<Area<100	-	-	1	-	M	-
	-	*Oscipital*	13<Area<100	-	-	1	-	M	-
	-	*Temporal*	13<Area<100	-	-	1	-	M	-

Table 1 shows the 9-segment index resulting from this study. In the first column, there are indexes number that refers to where the segment is located. Index 1 shows the location of hotspots in the right upper limb bone segment, and index 2 shows the location of hotspots in the left upper limb bone segment, index 3 is for the location of hotspots in the right lower limb bone segment, and so on. The indexes in Table 1 and Table 2 are in the anterior position, while the posterior part still use the same index, the difference is in the order in which the index number is read when the program is run.

The second column in the table is the location of the presence of hotspots in a segment. For example, we could find hotspots on the humerus (arm) both on the left and on the right in the anterior and posterior positions. The third column shows the values for the pixel area size range. The fourth column refers to the location of the presence of hotspots that appear on the part with symmetrical or asymmetrical sites. The fifth column is the density level of the object, to determine the density it falls into the “high” or “low” category previously described. The sixth column refers to the conclusion of the overall analysis result and prediction. The interface of the program designed in this study is shown in Figure 1.

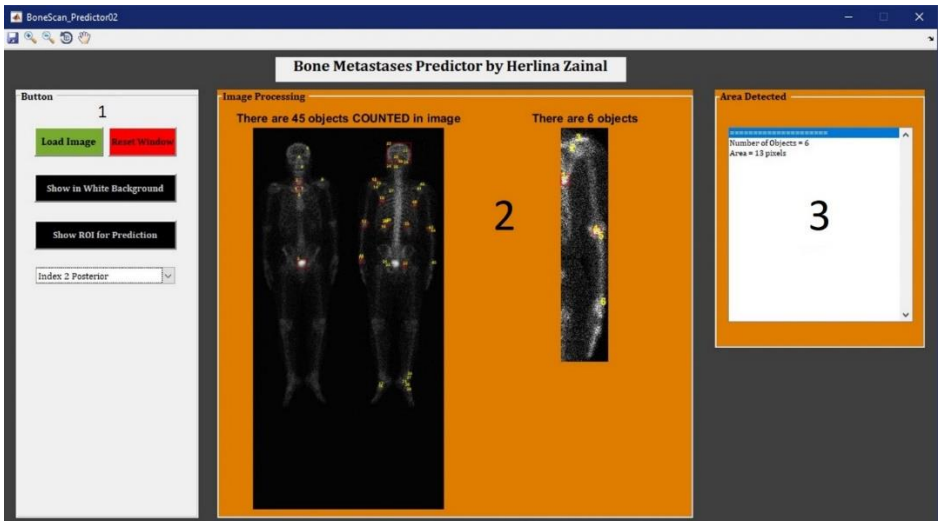
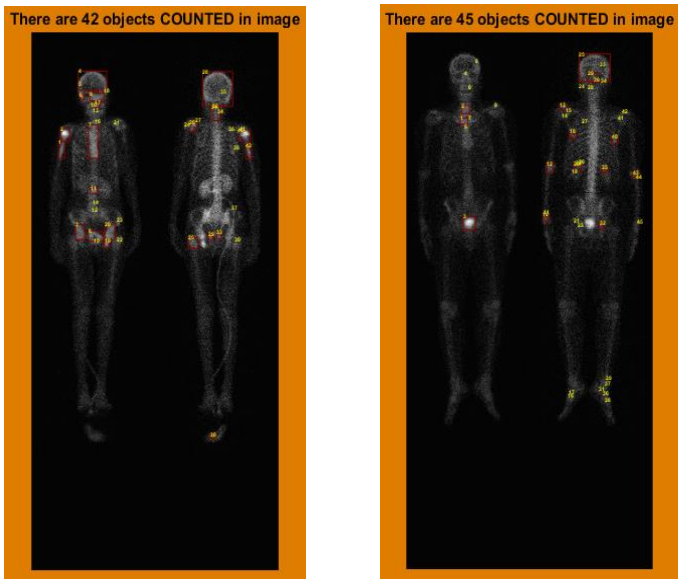


Figure 1. The user interface of the program.

In Figure 1, the part labeled number 1 is a panel button that contains command buttons to run the program. The window on the right is used to display an index or image segment which has also been processed by the same digital image processing technique. This section is designed to validate hotspots or objects that are not yet clear whether there are metastases or not. In the panel labelled with number 3, displays a window that contains information on pixel size and the number of objects read in the window on the right in panel 2.



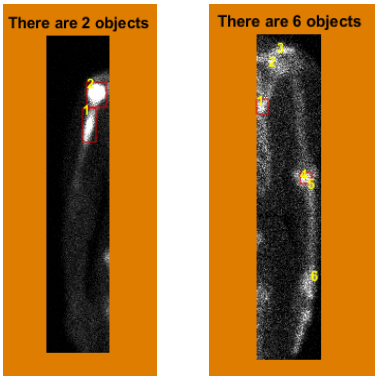
(a) **(b)**

Figure 2. The results of the prediction program, for patients: (a) with a diagnosis of metastasis, (b) with a normal diagnosis

Figure 2, shows a screenshot of the results of the prediction program for the determination of the presence of bone metastasis, referring to the inclusion and exclusion criteria, as mentioned before. The image of a patient diagnosed with metastasis will show hotspots whose presence met the inclusion and exclusion criteria, as in Figure 2(a). Based on the medical record data, this patient was a patient with a diagnosis of metastasis. After prediction using the program, the parts caught as hotspots are in an asymmetrical area and are not a joint area. This location has a higher

density compared to other joint sites. For validating the locations that are still uncertain, we analyze it by running the 9-segment index sub-program as seen in Figure 3(a).

Figure 2(b), the part of the bone marked with ROI and number label, is in a symmetrical area and is the location of the joint. The object that is caught is not a metastasis, but the result of degenerative disease at that location. Validation was then carried out to confirm the prediction by running the 9-segment index sub-program, as shown in Figure 3(b) below.



(a) **(b)**

Figure 3. Validation results with the 9-segment index sub-program: (a) patients with a diagnosis of metastasis, (b) patients with a normal diagnosis.

The user can take advantage of this program to predict hotspots at locations that are still uncertain at the time of visual analysis, by reviewing objects or hotspots using a predefined 9-segment index, before performing more complex examinations.

Bone scan examination has high sensitivity, but it doesn't have sufficient capability to distinguish whether the object is metastasis or not. It is because the resulting image from the examination does not have good intensity. According to this research, the significance level obtained by this program is 5%, corresponding to the results of the diagnosis obtained from the medical record data of the patients (85.67% ± 12.71%). This value is obtained from the mean and standard deviation of the comparison between medical record data and the predicted results of the program. The error that still often occurs is the noise that is captured during an examination. Especially in the bones of the head and spine area will be read as hotspots, even though it is not. This error was caused by the distance between the patient's position during the examination and the gamma camera was too close.

4. Conclusion

Prediction of the presence of bone metastasis by quantitative analysis using digital image processing techniques can be made. With a significance level of 5%, the prediction results using the analysis system design are compatible with the results of the diagnosis obtained from the medical record data of the patient of (85.67% ± 12.71%). The object that is metastatic can be determined by validation using a 9-segment index from the anterior and posterior positions: on the right and left upper limb bones, right and left lower limb bones, right and left ribs, spine, bones in the pelvic area, and bone segment in the head area.

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