

# CADBOSS: A computer-aided diagnosis system for whole-body bone scintigraphy scans

## ABSTRACT

**Aims:** The aim of this study is to develop a computer-aided diagnosis system for bone scintigraphy scans (CADBOSS). CADBOSS can detect metastases with a high success rates. The primary purpose of CADBOSS is as supplementary software to facilitate physicians' decision making.

**Materials and Methods:** CADBOSS consists of various elements, such as hotspot segmentation, feature extraction/selection and classification. A level set active contour segmentation algorithm was used for the detection of hotspots. Moreover, a novel image gridding method was proposed for feature extraction of metastatic regions. An artificial neural network classifier was used to determine whether metastases were present. Performance evaluation of CADBOSS was performed with the help of an image database which included 130 images (30 non-metastases and 100 metastases) collected from 60 volunteers. All images were obtained within approximately 3 hours after injecting a small amount of radioactive material  $^{99m}\text{Tc}$ -MDP into the patients and then carrying out scanning with a gamma camera. The 10-fold cross-validation technique was used for all tests.

**Results:** CADBOSS could correctly identify in 120 out of 130 images. Thus, the accuracy, sensitivity, and specificity of CADBOSS were 92.30%, 94%, and 86.67%, respectively. Moreover, CADBOSS increased physicians' success in detecting metastases from 95.38% to 96.9%.

**Conclusions:** Detailed experiments showed that CADBOSS outperforms state-of-the-art computer-aided diagnosis (CAD) systems and reasonably improves physicians' diagnostic success.

**KEY WORDS:** Artificial neural network, bone scintigraphy, computer-aided diagnosis, image processing

## INTRODUCTION

Cancer is one of the leading causes of death around the world. In recent years, it has become one of the greatest health concerns, and its incidence of cancer is increasing on a daily basis.<sup>[1]</sup> It can occur in any person from any age-group or gender, but is most often observed in middle-aged or older adults. Thus, age is an important factor in the development of cancer.<sup>[2]</sup> According to statistics published by international health organizations, there were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 years of diagnosis) throughout the world in 2012. Moreover, 57% (8 million) of new cancer cases, 65% (5.3 million) of cancer deaths, and 48% (15.6 million) of the cases of those who had been living with cancer for 5 years occurred in the less developed countries. Sixty percent of the world's total new annual cases occur in Africa, Asia, and Central and South America. Furthermore, 30% of cancer cases could be prevented, and this figure is markedly

increasing. It is presumed that 12 million people will die because of cancer by 2030.<sup>[1]</sup>

Metastases are the main causes of death due to cancer, and may affect any part of the body. One of the main targets of metastases is the skeletal system, and their detection has an important effect on treatment.<sup>[3]</sup> For example, approximately 3–10% of patients of breast cancer present with metastatic disease,<sup>[4]</sup> representing a high rate. Furthermore, especially with the help of early detection, most cancer cases can be cured through surgery, chemotherapy, or radiotherapy methods. It is important to take advantage of recent technological advancements to carry out diagnosis and early detection, which are crucial factors in the treatment of cancer. Bone scintigraphy is one of the well-known methods used to evaluate metastases, and is an effective, accurate, and valuable method. In addition, it is the most widely used diagnostic procedure in nuclear medicine.<sup>[5,6]</sup> However, there are some difficulties related to the detection of metastases via bone scintigraphy. First,

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the resolution quality of whole-body scintigraphic images is usually low, within the range of 5–10 mm, which is lower than the resolution quality of computed tomography. Second, the intensity range of the images is quite large, which is heavily related to the weight and tissue uptake factors of the patients, as well as certain clinical factors such as injection dose and time and radiopharmaceutical application.<sup>[7]</sup> Moreover, it is important to note that the interpretation process for the images is quite difficult and complex. Radiologists have to spend more time at work, since cancer spreads rapidly. Radiologists must be very careful in the interpretation and diagnostic process of cases, and should not allow any incorrect diagnosis in the course of the disease.<sup>[8]</sup>

Since the diagnostic process is very complex and takes lots of time, radiologists put a lot of effort into it. If they have to look at too many images they will make more mistakes.<sup>[6]</sup>

Developing a computer system that warns the radiologist about a suspicious diagnosis can be an effective way of sifting through imaging data. In a computer-aided diagnosis (CAD) system, the diagnostic imaging is integrated with computer science, pattern recognition, artificial intelligence technologies and image processing.<sup>[1]</sup> In recent years, CAD systems have attracting not only the attention of researchers, but also that of radiologists. However, CAD systems must be considered as a supplementary tool to assist the specialists, not as something that can replace their interpretation in the diagnosis.

The number of the studies focusing on CAD systems used for whole-body bone scanning is increasing on a daily basis. Huang *et al.*<sup>[9]</sup> developed a CAD system founded on anatomical knowledge-based image segmentation and a fuzzy set histogram threshold methods with a 92.1% sensitivity rate and 7.58 false detection/patient number in the scanned images. In the decision support system developed by Ohlsson *et al.*,<sup>[10]</sup> individual hotspots were detected and classified according to whether they were metastatic. The test sensitivity and specificity of this system were 95% and 64%, respectively. Erdi *et al.*<sup>[11]</sup> developed another semi-automatic CAD system using the region growing method, where the physician places a seed into a specific bone lesion then the computer system grows the lesion area in order to estimate the survival time of patients diagnosed with prostate cancer.

In a study conducted by Yin and Chiu,<sup>[12]</sup> a characteristic point-based fuzzy inference system (CPFIS) was used in order to locate the bone lesions. Radioactivity brightness and asymmetry were the two information inputs chosen for CPFIS. These inputs were considered to be specialised training tools for physicians. Whole-body bone images were segmented into six parts in this system as follows: Chest, head, vertebra, pelvis, hand, and leg. In addition, different systems were applied to each part. The sensitivity rate of the system is 91.5%, while the mean number of the false positives (FPs) is 37.3 lesions per image.

Sajn *et al.*<sup>[5]</sup> developed a methodology based on robust knowledge to detect the reference points in the main skeletal regions, which are used for auto-segmentation of the skeleton. The support vector machine (SVM) and ArTEX algorithms were applied for diagnosis. The sensitivity rate of the system is 79.6%, while the specificity rate is 85.4%. This system is the first completely automated method of carrying out whole-body bone scan diagnoses. Furthermore, Sadik *et al.*<sup>[13]</sup> developed a set of segmentation algorithms and used an artificial neural network (ANN) for the detection of bone lesions. For these neural networks, they employed 14 features as the input. The sensitivity rate of this system is 90%, while the specificity rate is 74%. According to Horikoshi *et al.*,<sup>[14]</sup> CAD software trained with a Japanese database showed much higher performance than the CAD software trained with a European database in terms of bone scans. The reason for these different results might have been physical differences between individuals in the two different nations, as well as different judgments concerning count intensity of the hotspots. In the approach of Al-Rifaic *et al.*,<sup>[15]</sup> which is a promising method that exhibited a similar rate of sensitivity, the stochastic diffusion search swarm intelligence algorithm was used as a tool to detect metastasis. This method has also been used for the training and teaching of medical students and junior doctors.

The ANN-based bone scan index, which shows the amount of bone metastasis, was developed by Nakajima *et al.*<sup>[16]</sup> This method has exhibited good diagnostic accuracy and reproducibility. However, it is probably affected by the training databases. The aim of this study is to revise the software by using a large number of samples from Japanese databases and obtaining valid diagnostic accuracy compared with the Swedish training database. Another study conducted by Tokuda *et al.*<sup>[17]</sup> aimed to investigate the diagnostic capability of a completely automated computer-aided system which detects metastases in the images of bone scans by focussing on two different patterns, as follows: First, it detects them per region; and second, it detects them per patient. The system is called “BONENAVI version 1.” According to the results, a new CAD system must decrease the number of FP findings, which depends on the primary lesion of the cancer.

The abovementioned studies exhibited low specificity. The aim of this study is to develop a more reliable, faster CAD system which can detect the metastases with high sensitivity and specificity, as well as justifiable FP rates. To satisfy the clinical requirements, such as reliability and rapidity, we propose a lightweight CAD system for whole-body scintigraphy scans (CADBOSS).

## MATERIALS AND METHODS

### Patients

The study population consisted of 160 images of whole-body bone scans from 60 patients who underwent bone scintigraphy for bone metastatic diseases from 2003 to 2013.

The cases included chest, prostate, and lung cancers, which are the most common cancers in Turkey. Technically, suitable images were used in the study; some of the images were excluded from the study population due to low resolution and mistaken scans. The system was created using 130 images, where 100 out of 130 images contained metastases. Ten-fold cross validation was used during the training and test phases. Sixty percent of the patients were males, and the average age was 57 years, with a range of 30 to 87. Most of the patients were over 55 years old. Twenty out of 60 patients did not have metastases. Bone scintigraphy images were performed using 740 MBq (20 mCi) Tc-99m MDP. Images were obtained 3 hours after 99mTc-MDP injection using a 15 cm/min rate throughout the entire body for at least 500,000 counts. Whole-body images, including anterior and posterior views, were obtained by using a  $\gamma$  camera. The resolution of the images was  $256 \times 1024$  pixels. The characteristics of the study population are given in Table 1.

The final evaluations of the patients were carried out by an experienced physician to determine whether they had bone metastases. These assessments were performed depending on the intensity and size changes, increasing and decreasing values of high accumulation areas, medical records of the patients, results of laboratory tests, and other accessible radiographic images. Grade 1 and 2 diagnostic criteria were applied for the final clinical evaluations<sup>[8-18]</sup> as follows:

Grade 1: If there was no bone metastasis observed, then the scintigraphy pattern was either normal or exhibited typical hotspots of the fractures or degenerate changes. Therefore, it could be concluded that there was no radiographic or clinical data suggesting bone metastases; and

Grade 2: There was a potential for bone metastases, since localised, distributed, and high-intensity hotspots were observed. These hotspots are not typical degenerate fractures or changes. Thus, it could be concluded from the clinical assessment that there were bone metastases.

## CADBOSS

CADBOSS consists of hotspot segmentation, feature extraction, feature selection, and classification section. A block diagram of CADBOSS is shown in Figure 1. The method used for hotspot segmentation is the level set active contour. After detection of hotspots with segmentation, feature extraction is carried out. The number of features was decreased by using the principal component analysis (PCA) method, as too many features would

**Table 1: Study population**

Parameter	Values
Number of patient	60 (40 abnormal, 20 normal)
Sex	36 Male, 24 Female
Mean age for patients	57 (range, 30-87)
Number of images	130 (100 metastasis, 30 non-metastasis)

affect the system negatively. In the final stage, images are classified as demonstrating or not demonstrating metastases with the ANN.

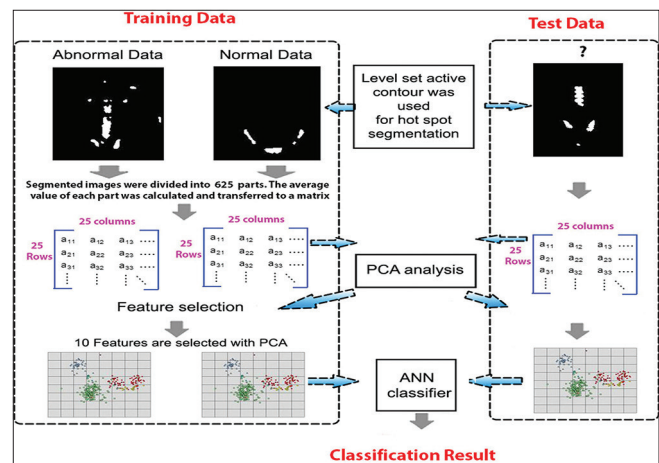
## Segmentation of hotspots

Hotspots in scintigraphy images appear as bright whiteness. Tumors, fractured bones, joints (knee, elbow, etc.), shoulders, or the bladder are hotspots, and are very bright in the images. To make a decision about metastases, it is first necessary to differentiate hotspots from the skeletal system. One of the most appropriate methods for doing so is segmentation. However, there is no segmentation method suitable for all types of images; rather, each medical image requires a different solution.<sup>[19]</sup>

In this study, we investigated popular segmentation algorithms such as self-organizing map (SOM), level set active contour (LSAC), fuzzy-cmeans (FMS), and k-means for the hotspot differentiation. However, the SOM and LSAC methods are the two methods that have attracted the most attention. It was observed that the LSAC method gave the best results. There are various modified active contour models in the literature. In this study, we used a model developed by Chunming Li which is capable of segmenting homogeneous images by their intensity.<sup>[20,21]</sup> Segmentation examples for the LSAC method can be seen in Figure 2. While testing the segmentation algorithms, images of the pelvis, chest, and thorax were used, as well as whole-body-scan images.

## Feature extraction and selection

Before applying whole-body bone scans to ANN, images were digitalized by performing feature extraction and optimized for classification. During the segmentation process, whole-body images were converted to binary images. A pixel valued at "0" was determined to be black and pixel valued at "1" was determined to be white. However, the sizes of the images were quite high for the neural network input. Therefore, the whole-body images were reduced to  $200 \times 700$  pixels. We



**Figure 1: Block diagram of computer-aided diagnosis system for bone scintigraphy scans (CADBOSS)**

created sub-images by dividing each image into 25 equal pieces horizontally as well as vertically, instead of giving the whole image to the ANN directly. Thus, we obtained 625 sub-images with a size of  $8 \times 28$  pixels. We call this process "image gridding." The gridding process made the images more favorable and lightweight for the ANN. Figure 3 shows the creation of the ANN input value from bone scintigraphy images by gridding.

On the other hand, using 625 inputs could have negatively affected the accuracy and duration of the process. There were many black pixels are observed in the background of the bone scintigraphy images due to the structure of the images. This negative factor affected the achievement of the study. Selecting only the needed inputs with no background pixels among these 625 sub-images would increase the accuracy of the study. In this context, the average value of each entry input was transferred to a matrix. PCA was used to find the most important values in accordance with the transferred values in the matrix. PCA is a general-purpose feature extraction method and one of the statistical methods that is used to reduce the size of input variables containing complex information.<sup>[22]</sup> Ten important features were selected amongst the 625 values transferred to the matrix by PCA because the performance results of system were obtained for these values; these were then used in the ANN as input patterns.

### The artificial neural network

After feature selection was performed using PCA, the next step is to detect the presence or absence of metastasis in the images. Machine learning algorithms have been successfully applied to many bioinformatics applications, including the diagnosis of breast, lymphoma, ovarian, brain, and lung cancers, as well as leukemia.<sup>[23]</sup> ANNs represent the preferred machine learning method for classification problems. In this study, a feed forward multi-layer perceptron-based ANN (FF-ANN) model was used. Multi-layer networks use a variety of learning techniques; one of the most popular is back-propagation. In this study, there were three layers,

namely the input, hidden layer, and output. Only one hidden layer was used, and 12 neurons were located in it. Ten inputs were obtained by the feature selection from bone scintigraphy and used as digital inputs to the ANN. We used two outputs, as follows: "1" represented metastases and "0" represented no metastases. Figure 4 shows the proposed ANN model.

### RESULTS

In order to evaluate CADBOSS, 130 whole-body scintigraphy images collected from 60 volunteers (40 patients with metastases, 20 healthy participants) were used. These images were obtained from Medical Faculty of Suleyman Demirel University, Konya Education and Research Hospital. If the radioactive material dose amounts were equal for all of the participants, this would mean that the intensity differences in high accumulation areas had to be due to the physical condition of the individuals. Accordingly, the amounts of the doses were similar in the images that we obtained from the two different facilities and used in the study.

The performance of CADBOSS was compared with the physician's judgments alone and physician + CADBOSS. No extensive differences were observed between the three systems. As shown in Table 2, CADBOSS classified 37 of the patients with metastases correctly as Grade 2, whereas 3 were incorrectly classified as Grade 1. The physician classified 38 of the patients with metastases correctly, whereas 2 were classified incorrectly. However, the physician increased the detection success in conjunction with CADBOSS. In this case, 39 patients were diagnosed correctly as having metastases, while only 1 case was misdiagnosed. Considering non-metastatic cases, 2 of 20 patients were misdiagnosed by CADBOSS. The physician also misdiagnosed one case, but the physician + CADBOSS diagnosed all non-metastatic cases correctly.

The confusion matrix of CADBOSS and the physician per image is shown in Table 3. According to the results, 94, 96, and 97

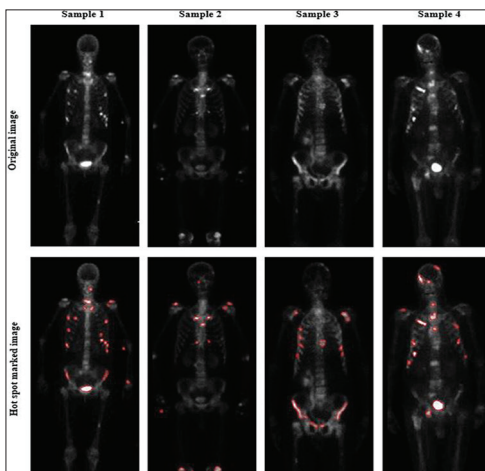


Figure 2: Examples of hotspot detection

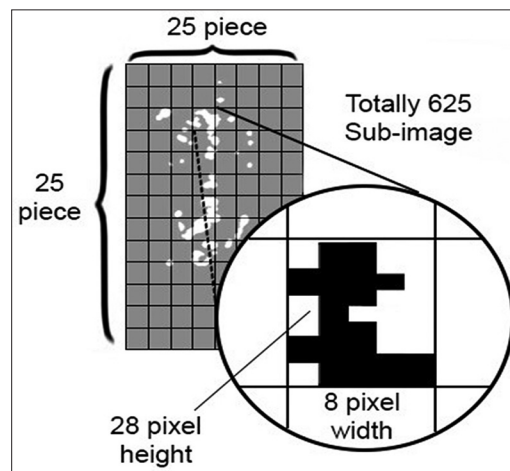


Figure 3: Image gridding for feature extraction

of 100 images were diagnosed correctly by CADBOSS, the physician, and CADBOSS + physician, respectively. Moreover, CADBOSS decreased the false positive and negative diagnoses of the physician.

The sensitivity, specificity, and accuracy of CADBOSS, the physician and both together are shown in Table 4.

One of the important performance evaluation criteria is receiver operating characteristic (ROC) graphs. In general, performance analysis of classification systems can be carried out with ROC using plots for the true positive rate (sensitivity) and FP rate (1-specificity). The ROC curves of CADBOSS, the physician, and both together are shown in Figure 5.

**DISCUSSION**

CADBOSS brings a new perspective to the CAD systems which have been designed for bone scintigraphy. Unlike many other studies in the literature, instead of segmenting the skeletal system anatomically, it focuses on directly segmenting the

hotspots. The results of hotspot segmentation are input into the ANN. This property makes CADBOSS lightweight, rapid, and more accurate. CADBOSS shows a high detection rate, with a sensitivity of 94% and specificity of 86.67%. The results that we have obtained are better than the state of the art CAD system in the literature. A comparison is given in Table 5.

The aim of CAD systems is to assist physicians to enhance their performance by combining their knowledge with the software tools, not to replace physicians. It is important for CAD systems to determine whether metastases are present. More importantly, a CAD program must show all the hotspots which a physician might not notice, as the human brain is capable of remembering and interpreting visual items much better. The suggested CAD system marks hotspots with different colors in the evaluated images. This marking system is an important factor that saves a lot of time of the physician. We used only a two-point scale, where images were categorised as Grade 1 or Grade 2, unlike in the most referenced studies. However, a two-point scale is more realistic, physicians generally use two categories, namely the absence and presence of metastases.

Our bone scintigraphy images had a poor resolution due to the gamma camera. Poor image resolution makes the evaluation of images more difficult. Our system could give better results if the camera were more technologically advanced. On the other hand, our database came from only two hospitals; a larger experimental group would improve the accuracy of the results.

The images were evaluated by one experienced physician. If more physicians had evaluated the performance of CADBOSS, the results would have been more realistic. Moreover, for more reliable assessment, CADBOSS should be tested in a clinical setting.

The performance of CADBOSS was measured according to the determination of bone metastases for multiple types of

**Table 2: Confusion matrix of computer-aided diagnosis system for bone scintigraphy scans and physician (per patient)**

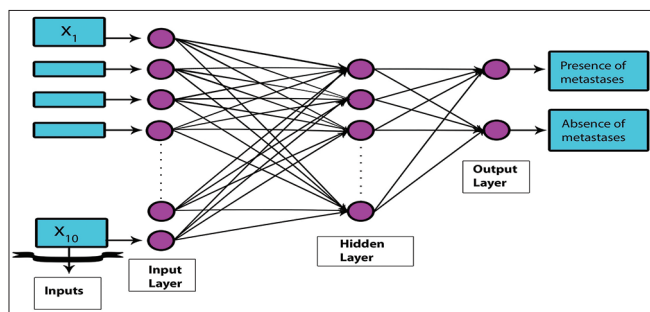
	CADBOSS		Physician		CADBOSS+ physician	
	T	F	T	F	T	F
P	37	3	38	2	39	1
N	18	2	19	1	20	0

P=Positive, N=Negative, T=True, F=False, CADBOSS=Computer-aided diagnosis system for bone scintigraphy scans

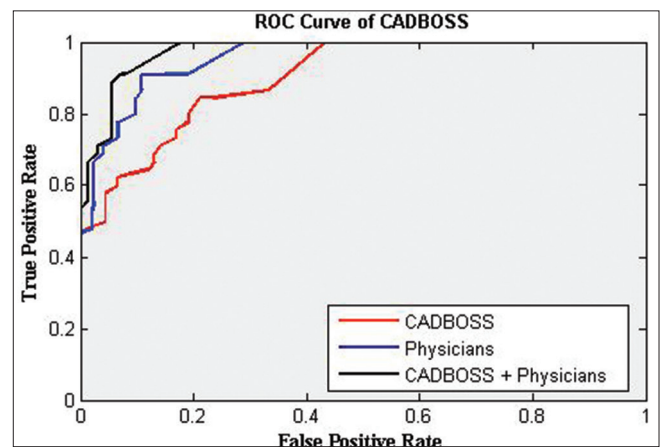
**Table 3: Confusion matrix of computer-aided diagnosis system for bone scintigraphy scans and physicians (per image)**

	CADBOSS		Physician		CADBOSS+ physician	
	T	F	T	F	T	F
P	94	6	96	4	97	3
N	26	4	28	2	29	1

P=Positive, N=Negative, T=True, F=False, CADBOSS=Computer-aided diagnosis system for bone scintigraphy scans



**Figure 4: The feed forward multi-layer perceptron-based artificial neural network (FF-ANN) architecture of computer-aided diagnosis system for bone scintigraphy scans (CADBOSS)**



**Figure 5: Receiver operating characteristic (ROC) diagram for computer-aided diagnosis system for bone scintigraphy scans (CADBOSS) and physician**

**Table 4: Performance criteria of computer-aided diagnosis system for bone scintigraphy scans and physicians**

Perf. crit.	CADBOSS	Physician	CADBOSS+physician
Accuracy	92.3	95.38	96.9
Sensitivity	94.0	97.95	98.0
Specificity	86.67	87.5	90.6

CADBOSS=Computer-aided diagnosis system for bone scintigraphy scans

**Table 5: The comparison of computer-aided diagnosis system for bone scintigraphy scans and the other computer-aided diagnosis (CAD) systems**

Perf. crit.	CADBOSS	May sadik <sup>[5]</sup>	Hiroyuki horikoshi <sup>[13]</sup>
Sensitivity	94	90	90
Specificity	87	89	81
Accuracy	92	89	82

CADBOSS=Computer-aided diagnosis system for bone scintigraphy scans

cancer (chest, prostate, and lung). However, it could also be evaluated separately for all cancer types.

## CONCLUSIONS

In this study, we designed a novel and fully automated CAD system for whole-body scintigraphy scans (CADBOSS). CADBOSS can identify hotspots with the help of the LSAC method. For hotspot classification, we proposed a simple but effective feature extraction method called image gridding. We used an FF-ANN architecture for the detection of metastases. CADBOSS can diagnose metastatic cases with a high success rates (accuracy, 92%; sensitivity, 94%) with the help of its lightweight but effective methodology. Therefore, it outperforms the state-of-the-art CAD systems. In addition, it can mark hotspots and draw physicians' attention via the graphical user interface. Thus, the physicians' successful detection of metastases may increase. As a result, the proposed CADBOSS facilitates physicians' decision making and can be used by physicians as a supplementary tool for the detection of metastases.

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