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A Thresholding Technique for Potentially Malignant Cells Recognition in Epithelial Tissues

Basim Alhadidi, Malik Braik and Mohammad I. Salem
Department of Information Technology, Al Balqa' Applied University, Salt, Jordan

Corresponding Author: Basim Alhadidi, Department of Information Technology, Al Balqa' Applied University, Salt, Jordan

ABSTRACT

In this study, a thresholding technique was proposed as a mechanism to recognize the malignant cells in epithelial tissues. This is particularly useful for cancer cells diagnosis. Malignant transformation is a genetic operation that causes changes in cells morphology and behavior. Therefore, the evaluation of changes in the cell biology was studied in a way to find out the basis for diagnosing such diseases. The proposed thresholding technique depends on the automation of counting black to white cells ratio and the number of cells in the epithelial tissues samples. This technique has many features, such as: it is able to test hundreds of samples in a less computing time and can provide reliable results and it can give the user a better control over the counting process and can process any part of the sample. The results obtained in this study confirmed the potential of the proposed technique, such that it can judge the malignant cells in epithelial tissues whether normal, abnormal or suspected only in few seconds. Using threshold technique in diagnosing epithelial tissues samples can provide fast and easy way to perform malignant diagnosis (normal, abnormal or suspected) to be used as reference for early diagnosis medical research.

Key words: Malignant cells, epithelial tissues, gray threshold, nucleus cells, image enhancement

INTRODUCTION

Worldwide, oral carcinoma is one of the most prevalent cancers and one of the most ten common causes of death (Alhadidi and Husam, 2008; Mohammad, 2009). Carcinogenesis is a genetic process that makes many changes in the construction and behavior of the malignant cells. These changes at the molecular level may make the primary means of diagnosis and management (Worz and Rohr, 2006). Since these changes mediate morphologic changes that occur after genetic changes based on the subjective assessment, thus knowledge of current morphologic changes of cell construction and histopathology changes is needed (Jackson *et al*., 2006; Kaderali *et al*., 2006). Epithelial dysplasia is the tissue that is located in the cervix; it leads from the uterus into the vagina, also it can be on the lateral/ventral tongue. Epithelial dysplasia is shown in Fig. 1 and 2 (Manoli *et al*., 2006).

The malignancy epithelial tissues have many common features (Chanel *et al*., 2007; Kaderali, 2007; Ulrich *et al*., 2006); they are:

- **Pleomorphism:** It is the occurrence of two or more structural forms during a life cycle
- **Hyperchromasia:** It is the descriptive term that refers to the hyperchromatic state of the nucleus, the hyperchromatic state of the nucleus suggests malignancy (very dark nucleoli due to the increased chromatic Deoxyribo-Nucleic Acid (DNA) content)

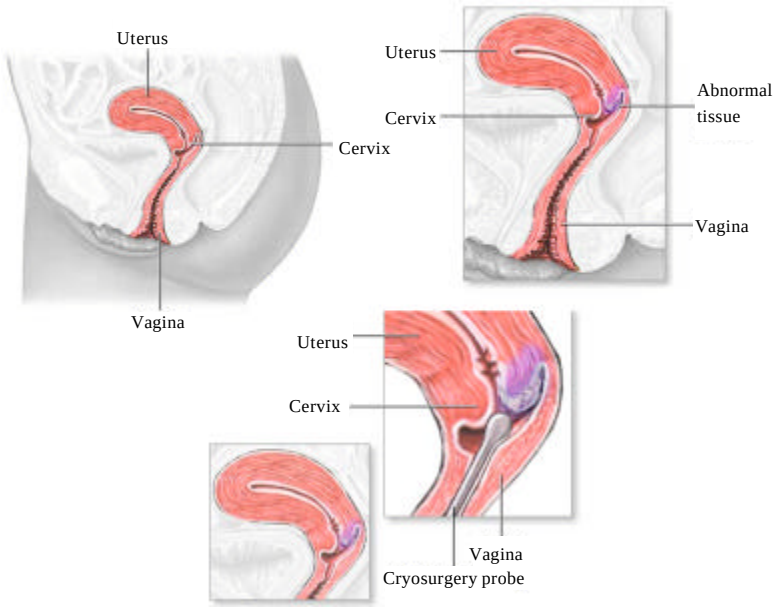

Fig. 1: Epithelial dysplasia, the tissue that leads from the uterus into the vagina (Regesi and Ma, 2000)

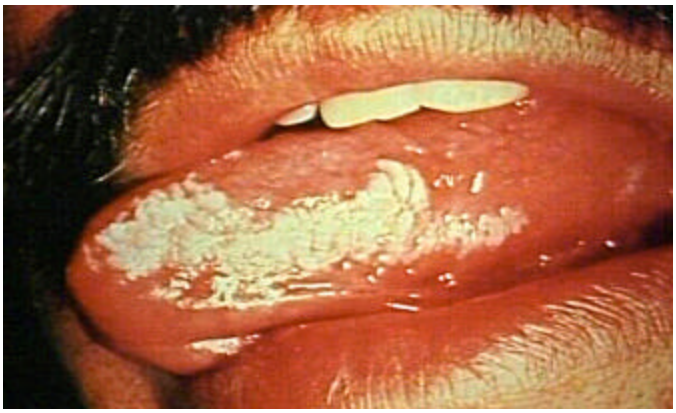

Fig. 2: Epithelial dysplasia tissues on the lateral/ventral tongue (Regesi and Ma, 2000)

- The nuclear to cytoplasmic ratio may approach 1:1 instead of 1:4
- Numerous and typical mitotic: it is the process such that the cell separates the chromosomes into two identical sets. An example of non-malignant and malignant cells is shown in Fig. 3

Now-a-days most diagnosis processes are depending on complicated laboratory procedures; these procedures cause more wasting time, also they are susceptible to errors (Silverman *et al*., 2001a). A substantial body of this work has been compiled to determine the progressive nature of premalignant cells to become malignant. However, it is not often possible to identify cell lesions

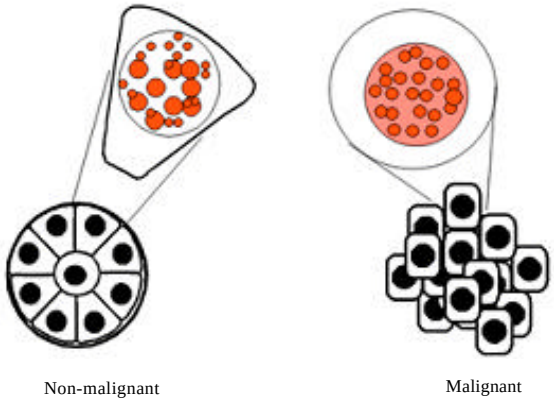

Fig. 3: Non-malignant and malignant cells

which will follow a progressive course or to distinguish them from those which are regressive in nature based only on pure morphological criteria (Silverman *et al*., 2001b). The proposed study in this study aims to facilitate the recognition of early malignant changes in the epithelial cells based on the number of tumor cells. Those highly active cells contain significantly larger amount of DNA than normal cells which leads to increasing the size and number of nuclei within the tissues (Bindu *et al*., 2006). The study compares the number of zeros pixels to the number of ones and then calculates the number of pixels in the image and based on the results, the malignant cells can be correctly distinguished.

PROPOSED THRESHOLDING ALGORITHM

In this study, a new methodology for malignant cells recognition has been proposed, the proposed system is divided into three main parts in succession. At the beginning the image is enhanced based on some criteria methods, then the image is segmented using a global thresholding technique and finally, the ratio of black to white nucleus and the number of nucleus are counted as the bases for the recognition process since tumor cells displayed stronger staining compared with normal mammary epithelial cells (Zia *et al*., 2007). The concept of automatic recognition for early malignant changes in the epithelial cells was developed on the images acquired from microscopic photographs. The presented approach based thresholding technique has the purpose of distinguishing malignant cells in epithelial tissues. This can provide an easy way of diagnosing cancers cells. Figure 4 shows the entire stages of the proposed method.

It can be seen from Fig. 4 that the proposed algorithm consists of three phases: Enhancement phase which consists of the median filter followed by contrast stretching method, then, segmentation phase which consists of global gray-thresholding technique and finally, the recognition phase based on the cells values within the tissues of the sample images. Most epithelial carcinomas exhibit similar cell characteristics because of the similar embryonic origin (Alhadidi and Husam, 2008; Mohammad, 2009), therefore, each sample image must pass through those phases in order to determine whether the malignant cells have a cancer or not, or can be suspected to a cancer. However, the general outline and details of the proposed thresholding algorithm will follow the description below.

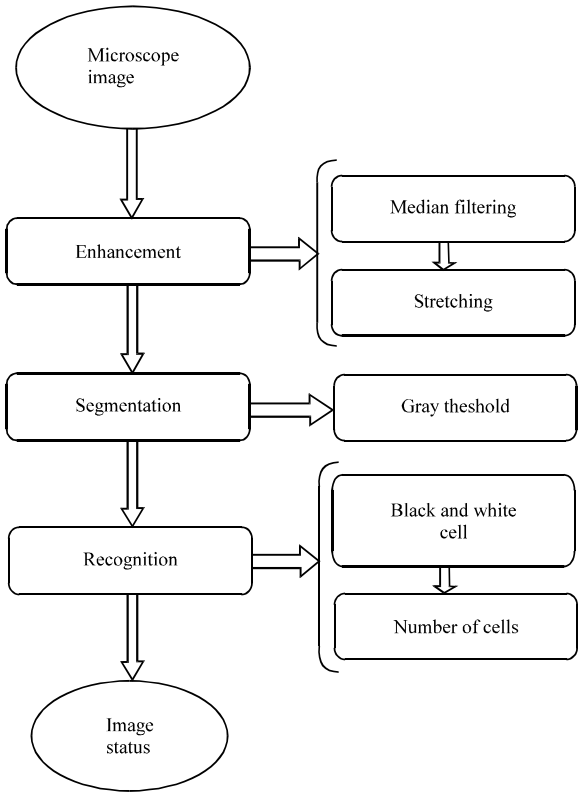

Fig. 4: Proposed malignant cells recognition system

IMAGE ENHANCEMENT

Microscopic images are usually affected by noise which devastates radiometric resolution and incapacitates the task of human interpretation and scene analysis. Reducing the noise and smoothing the images are the most important steps before the segmentation and recognition processes. Hence, the natural variations and noises inside the images will disturb the segmentation process. Therefore, the quality of the segmented images is based on the filter type (Gonzalez and Woods, 2008; Bonnet *et al*., 2002). The enhancement methods are inquired about to improve the visual appearance of the images in order to obtain a required image perception (Gonzalez and Woods, 2008; Munteanu and Rosa, 2000). This can be accomplished by sharpening the image features and increasing the contrast, thus, it can improve the image quality and make it more useful for analysis (Gonzalez and Woods, 2008). This preprocessing phase must manage the effects of the noise and increasing the visuality of the image; therefore, it preserves the image features and thereby provides the foundation for a successful recognition.

The preliminary step of the enhancement phase is image adjustment for the original sample (Fig. 5a), the input image is adjusted to perform a number of intensity transformation operations, adjusting the image is performed using two steps: view the histogram of the image to determine the intensity value limits between 0.0 and 1.0. These intensity limits are specified using stretchlim function such that all the color levels are in the range between 0 and 255. The output of the image adjustment step using the specified range is shown in Fig. 5b.

Median filtering: Median filtering is a powerful filter for removing the noise from two-dimensional images without blurring edges. This makes it particularly suitable for enhancing microscope images

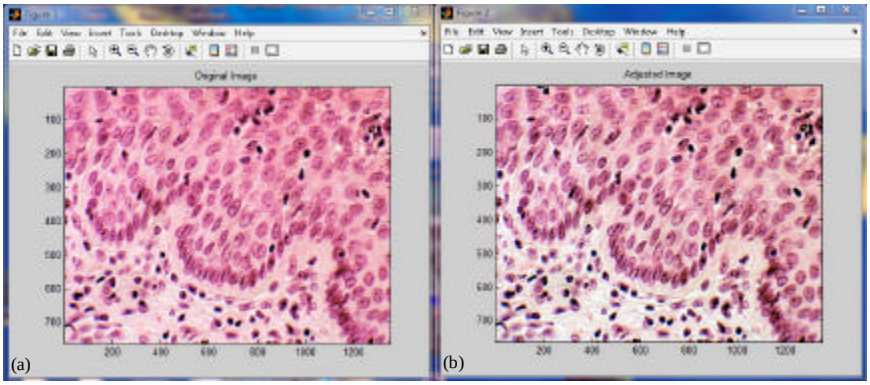

Fig. 5 (a-b): (a) (1349*762) Original mage and (b) (1349*762) Adjusted image. The post-processing steps of image enhancement phase are: Median filtering and contrast stretching

(Gonzalez and Woods, 2008). To apply median filtering to a medical image Fig. 6c, the low-frequency image is generated by replacement the pixel value with a median pixel value computed over a square area centered at the pixel location (Gonzalez and Woods, 2008; Mendez *et al*., 1996).

Contrast stretching: The simplest method to increase the contrast in the image is to adjust the histogram of the image, Fig. 6 d, such that there is a great separation between foreground and background gray level distributions (Gonzalez and Woods, 2008; Munteanu and Rosa, 2000). Applying contrast enhancement filters improve the readability of the low contrast areas in the image. Also, they will destroy areas of the image where the intensity of the pixels is outside the range of intensities being enhanced (Gonzalez and Woods, 2008; Li *et al*., 1996).

The designing function (f) in Eq. 1 can be used to rescale the output grayscale values such as (x) is the input image gray level:

$$f = \begin{cases} \alpha x & 0 \le x < a \\ \beta (x-a) & a \le x < b \\ \gamma (x-b) & b \le x < L \end{cases} \quad (1)$$

where, (f) shows a typical contrast stretching transformation of the gray levels distribution in the image. α, β and γ are chosen greater than unity in the region of stretch. The parameters (a) and (b) are obtained by examining the histogram of the original image. (L) Is the maximum gray level of the original image. The results of applying median filter followed by contrast stretching to a sample image are shown in Fig. 6 a and b.

The contrast stretching image shown in Fig. 6 can be easily analyzed by the human eye, the uniform distribution of the image histogram is considered as a probability distribution, it achieves the maximum entropy which contains the most information. Therefore, redistribute the gray levels to obtain a uniform histogram as possible and thus the image information should be maximized (Glasby, 1993; Chang *et al*., 1994). As seen in Fig. 6, the dynamic range of the gray levels in the image being processed using contrast stretching is increased. Therefore, the overall intensity and the information of the original image should also be increased.

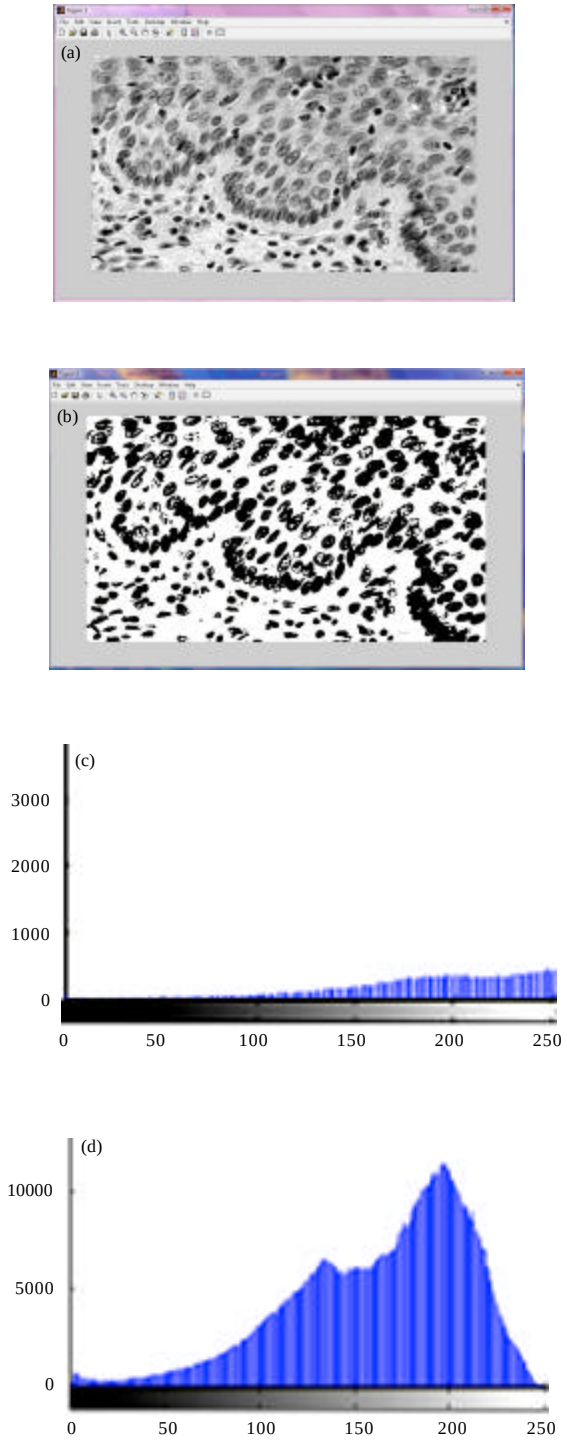

Fig. 6 (a-d): (a) (1349*762) Filtered image using Median filter, (b) (256*256) Contrast stretching image, (c) (250*4000) Resulted histogram of Median filter and (d) (250*12000) Contrast stretching histogram

IMAGE SEGMENTATION

The global thresholding level based graythresh function is computed to convert an intensity image to a binary image. The output binary image has two classes: White for all pixels in the input image with luminance greater than a specified level; and black for all other pixels. Accordingly, binary images are obtained by thresholding the grey level image. Pixels with grey level above the specified threshold are set to 1 whilst the rest pixels are set to 0. This can produce a white object on a black background, or vice versa, depending on the relative grey values of the object (Gonzalez and Woods, 2008). The graythresh function uses Otsu's method (Sezgin and Sankur, 2004). Otsu's method chooses the threshold to minimize the intraclass variance of the black and white pixels (Abutaleb, 1989). The graythresh function ignores any nonzero imaginary part of the image data (Chang *et al*., 1994). Otsu's method is used to automatically perform histogram shape-based image thresholding. The segmentation phase is performed by the following steps:

Step 1: The image matrix is converted to an intensity image with values in the range 0.0 (black) to 1.0 (full intensity or white)

Step 2: The global threshold level is computed using the global image threshold based Otsu's method. Level is a normalized intensity value that lies in the range [0, 1]

Step 3: The specified level is then used to convert the intensity image to a binary image by thresholding

The output image based the global thresholding technique using Otsu's method is shown in Fig. 7.

The thresholded image contains two classes of pixels, thus, the optimum threshold separating these two classes is calculated so that their combined spread intraclass variance is minimal. This phase is essential since it can help to check the value of each pixel based on some threshold value.

MALIGNANT CELLS RECOGNITION

Recognition accuracies are highly dependent on the feature set selection. In other words, classification accuracy is as good as the feature set that is selected to represent the images. For each sample, two values are calculated. The image is then classified to normal, abnormal, or suspected to cancer based on the selected criteria. These two criteria are:

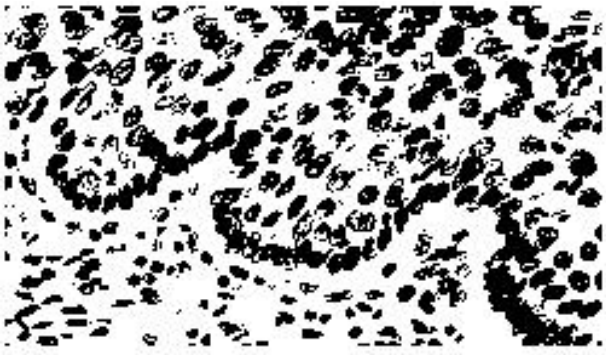

Fig. 7: (1349 * 762) The output segmented image

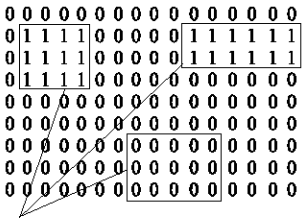

Fig. 8: Three connected component in a sub-image sample

Black and white ratio: This criterion can be computed by measuring the ratio of black area to white area in the sample image. This can be done by counting the number of ones and zeros in the sample image. Black and White Ratio (BWR) is defined as given in Eq. 2:

$$BWR = \frac{\text{No. of ones}}{\text{No. of zeros}} \tag{2}$$

This criterion does not give a final decision of the sample status; therefore, another criterion must be calculated.

Counting the number of nucleus cells: The Number of Nucleus Cells (NNC) criterion is based on counting the number of connected components in the sample image which represents the number of nucleus cells inside the sample image. A connected component in a binary image is a set of pixels that form a connected group (Gonzalez and Woods, 2008). Figure 8 shows a sub-image with three connected components.

The pixels belonging to each connected component are identified using the labeling procedure whereas, the connected component labeling is the process of identifying the connected components in the image and assigning each one a unique label (Gonzalez and Woods, 2008). The number of connected components in the image represents the number of nucleus inside the image.

In this study, as mentioned above we used the thresholding technique that is considered as one of the most used techniques in the medical field in terms of excellent findings. Some research have used same technique; as an example, in (Poonguzhali and Ravindran, 2008) Mammogram breast cancer images work with gray level values; the original image was segmented by threshold, edge-based segmentation and watershed segmentation. Threshold technique turned out to be the fastest segmentation with a poor output image, in the case of cancer detection using threshold technique; the core of cells is what was taken into consideration (black and white rations) for the number and size of cell's core.

In addition to this, other study has been conducted to answer similar questions using different techniques, some of these techniques are cited below:

Alhadidi *et al.* (2007) combined set of statistical and spectral texture parameters were employed to explore the possibility of an automatic classification of ultrasonic liver images. The combined features were used to classify these images into four classes: Normal, cyst, benign and malignant masses. It appears that cysts were the most homogeneous texture and distinct among the four classes using echo texture patterns using a custom designed back propagation neural network classifier where the features are extracted and given as an input to the neural network for

classification. The optimal selection process is carried manually to select the best features then the neural network will increase the classifier performance.

In the Computer Aided Diagnosis (CAD) (Sheshadri and Kandaswamy, 2006) the final diagnostic decision and the recommendation for an appropriate patient treatment are made by the radiologists to determine the true cluster case.

In each case then the system will be capable of detecting the micro calcifications in the digital mammograms (image segmentations) from the local background breast tissue.

The purpose of the system is to alert radiologists to suspicious areas on the mammograms. Using the same techniques used in image processing on a tissue sample, the suspicious areas are contracted regarding the original areas.

Statistical methods were used in by Nurhayati *et al.* (2010) to extract the texture feature of an image. Image characteristics such as the arrange pixel intensity and the texture feature namely contrast; entropy and homogeneity with other features were counted from the image intensity. The texture feature could be analyzed from an image to identify the characteristics of its surface. It is counted from a certain area and the resultant values were compared to the reference values. The measure of a feature object was done using image processing with Wiener filtering, histogram equalization and region growing methods to statistically feature of the thermograms.

Another research on mammography images using Morphological operators and Fuzzy c-means clustering for cancer tumor mass segmentation. The first step of the cancer signs detection should be a segmentation procedure that is able to distinguish masses and micro calcifications from background tissue using Morphological operators and finally fuzzy c-means clustering (FCM) algorithm has been implemented for intensity-based segmentation (Basha and Prasad, 2009).

DISCUSSION

The implemented application has two optional steps:

- For the purpose of magnification, the image can be of original size or lessened to 0.05 of its size. This step allows the user to reduce the size of the image for the analysis by deciding the magnitude of the image to be processed
- The second optional step allows the user to select a part of the image to be identified by the application

Therefore, some samples may comprise the whole image not only the area of malignant cells in epithelial tissues.

The recognition problem considered in this study is to determine the malignant cells using a thresholding approach. In order to evaluate the thresholding based approach, 20 sample images are selected for running the algorithm. As discussed previously, the proposed criteria to classify if the sample is suspected to cancer or free from cancer are black to white ratio and number of malignant cells. The results of black to white ratio are given in Table 1.

It can be observed from Table 1 that all samples (suspected to cancer or free from cancer) has white malignant cells more than black malignant cells, thus the ratio of black to white cells is less than 1 for all reported results in Table 1. Furthermore, some normal samples have ratios more than infected samples. The other criterion for recognizing the malignant expanding in the epithelial tissues is the number of cells in each sample image. The sample images with the number of nucleus cells sorted ascending are reported in Table 2.

Table 1: Samples ordered ascending by black to white ratio (BWR)

Sample name	BWR
Normal 04	0.17661
Normal 03	0.18101
Normal 01	0.28248
Normal 06	0.30142
Normal 09	0.32143
Abnormal 10	0.32378
Abnormal 12	0.32483
Abnormal 09	0.32701
Abnormal 06	0.33749
Normal 08	0.36773
Abnormal 01	0.40614
Abnormal 07	0.45549
Abnormal 08	0.46223
Normal 02	0.49096
Abnormal 11	0.53057
Abnormal 04	0.56114
Abnormal 02	0.58724
Normal 10	0.59465
Normal 05	0.6864
Normal 07	0.75162

Table 2: Number of nucleus cells in each sample image (NNC)

Sample name	NNC
Normal 05	49
Normal 07	54
Normal 02	112
Normal 09	132
Normal 01	270
Normal 10	274
Normal 03	301
Normal 06	527
Normal 08	528
Abnormal 12	554
Abnormal 11	558
Abnormal 02	559
Normal 04	576
Abnormal 01	664
Abnormal 04	674
Abnormal 10	871
Abnormal 06	1415
Abnormal 09	1462
Abnormal 08	1851
Abnormal 07	2386

The listed results in Table 2 indicates to the number of nucleus cells in each sample (infected or normal), moreover, the suspected samples to cancer have more cells in the image whilst the normal samples have less cells.

This intimation can provide the exact explanation of why we choose to compute the above criterion and also it help us to identify the malignant expanding in the epithelial tissues.

The preliminary results in Table 2 indicate that the proposed approach distinguishes the suspected images. However, the black and white ratio and number of cells criteria separately are not perfect criteria but they can give an indication of how to support a decision of the sample tissues in a more systematic way. However, both criteria combined reflecting precisely the detail content of the malignant tissues in the images.

Consequently, a good objective explanation can be derived from the above two criteria. This can be done by calculating the multiplication of the black and white ratio by the number of cells for each sample (BWR×NCC). Table 3 shows the multiplication of black and white ratio by the number of cells for each corresponding sample and the final results are reported in ascending order based on (BWR×NCC).

It can be concluded from Table 3 that increasing the number of nucleus pixels gives an indicator of malignancy diffusion. So, the results in Table 3 reveal the fact that the image contains the highest number of (BWR×NCC) can be rated highly as abnormal or having cancer. It is clear from Table 3 that the thresholding based approach gives the best detail information for determining if the sample image contains cancer or not or can be suspected to cancer. Moreover, based on the information given in Table 3, the range of samples diagnosis is derived as defined in Table 4. Finally, based on Table 3 and 4, the recognition of malignant cells in epithelial tissues of the testing samples can be clearly divided into three main categories:

Table 3: The black and white ratio times number of cells for each sample

Sample No.	Sample name	BWR×NNC
1	Normal 05	33.6336
2	Normal 07	40.58748
3	Normal 09	42.42876
4	Normal 03	54.48401
5	Normal 02	54.98752
6	Normal 01	76.2696
7	Normal 10	80.7341
8	Normal 04	101.72736
9	Normal 06	158.84834
10	Abnormal 12	179.95582
11	Normal 08	194.16144
12	Abnormal 01	269.67696
13	Abnormal 10	282.01238
14	Abnormal 11	296.05806
15	Abnormal 02	328.26716
16	Abnormal 04	378.20836
17	Abnormal 06	477.54835
18	Abnormal 09	478.08862
19	Abnormal 08	855.58773
20	Abnormal 07	1086.79914

Table 4: Samples diagnosis based on BWR combined with NCC

BWR×NCC	Samples diagnosis
1-149	Normal
150-270	Suspected to malignant cells
271 and more	Abnormal

- The samples from 1 to 9 are normal samples
- The samples from 12 to 20 are abnormal samples
- The samples from 10 to 11 are enigmatic samples, they are suspected to the malignant cells and cannot be recognized correctly, those samples contain features from the two classes: normal and abnormal. Therefore, another test must be applied to recognize those samples accurately

It can be inferred from Table 4 that when the value of (BWR×NCC) belongs to the range from 1 to 149, the samples can be diagnosed as normal samples and when the value of (BWR×NCC) is enclosed between 150 and 270, the samples are suspected to malignant cells and finally the abnormal samples have (BWR×NCC) exceeded the value of 271.

Derived from the last few paragraphs we can say that this approach can divide the list of samples in three ranges; normal samples, abnormal samples and third range for suspect samples, as shown in Table 4.

The study has focused on improving malignant diagnosis via image processing techniques, images are just data and image processing is simply manipulating that data. The recognition method is depending on the number of nucleus which is increased in the malignant tissues and the size of nucleus it self and this can be translated in the number of objects that remaining in the sample after image enhancement and the percentage ratio of black and white in all pixels that contained in the sample since that the increasing of black ration is the other indicator for malignant cells expanding in the tissue.

CONCLUSION AND FUTURE WORKS

In this study, an automatic recognition approach for malignant epithetical cells from digital microscope images has been employed where the outputs are encouraging and guaranteed to perfectly differentiate the cells. The approach used an evaluation criterion by specifying both of black and white ratio and number of nucleus cells. The objective of the algorithm is to determine whether the sample contains cancer or not, or can be suspected to cancer, thus being able to recognize the malignant cells in the medical microscope images. It was found that the approach can greatly recognize the malignant and the evaluation criteria have shown this algorithm's efficacy. The obtained results indicated that the proposed approach has a high effectiveness on a large category of microscope images. Future research will focus on how to implement the algorithm on parallel computing platform for enhancing, segmenting and recognizing microscope images. Also, another extension of the algorithm is to add another criterion to recognize the suspected images to be one of the two classes.

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