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A Study on Development of Automation Diagnosis of Liquid Based Cytology

(Suatu Kajian Pembangunan Diagnosis Automasi Sitologi berasaskan Cecair)

SEONG-HYUN KIM, HAN-YEONG OH & DONG-WOOK KIM*

ABSTRACT

Cervical cancer afflicts women worldwide. The patients' mortality with cancer has been increased by changing to westernized dietary habit and lifestyle. In order to detect early cervical cancer, a liquid-based cytology (LBC) was used to examine the exfoliated cells collected from the cervix. This procedure helps to decrease the mortality rate. However, this test mostly involves manual examination by the pathologists. This procedure needs to develop more efficient tool in detecting cervical cancer which rate kept increasing. As such, this study was designed to develop some methods to increase the effectiveness of LBC. The diagnosis algorithm was also established to diagnose the processed cell images via an imaging process algorithm based on the diagnosis criteria. A cell diagnosis program based on GUI, combined with the imaging process and the diagnosis algorithms were developed to automate the test process. The results of this studies showed that this new program can be used for effective diagnosis of cervical cancer. Moreover, it was deemed to increase the precision and accuracy of diagnosis and save patient time.

Keywords: Automation diagnosis; diagnosis algorithm; image processing algorithm; liquid based cytology (LBC); uterine cervical cancer

ABSTRAK

Kanser pangkal rahim menyerang wanita di seluruh dunia. Kematian pesakit kanser telah meningkat akibat penukaran tabiat pemakanan dan gaya hidup yang kebaratan. Untuk pengesanan awal barah pangkal rahim, sitologi berasaskan cecair (LBC) digunakan untuk mengkaji sel-sel yang dikumpul daripada serviks. Prosedur ini membantu mengurangkan kadar kematian. Walau bagaimanapun, ujian ini kebanyakannya melibatkan pemeriksaan secara manual oleh ahli patologi. Prosedur ini perlu membangunkan alat yang lebih cekap untuk mengesan kanser pangkal rahim kerana kadarnya yang semakin meningkat. Oleh yang demikian, kajian ini telah direka untuk mencadangkan beberapa kaedah untuk meningkatkan keberkesanan LBC. Diagnosis algoritma juga dibangunkan untuk mendiagnosis proses imej sel melalui suatu proses pengimejan algoritma berdasarkan kriteria diagnosis. Suatu program sel diagnosis berdasarkan GUI, digabungkan dengan proses pengimejan dan diagnosis algoritma telah dibangunkan untuk mengautomasikan proses ujian. Keputusan kajian ini menunjukkan bahawa program baru ini boleh digunakan untuk diagnosis kanser pangkal rahim dengan berkesan. Selain itu, ia dilihat boleh meningkatkan kepersisan dan ketepatan diagnosis dan menjimatkan masa pesakit.

Kata kunci: Algoritma pemprosesan imej; diagnosis algoritma; diagnosis automasi; kanser pangkal rahim; sitologi berasaskan cecair (LBC)

INTRODUCTION

According to the 2013 Causes of Death stated in The National Statistical Office of Korea (2012) report, the total death toll was 267,000 with a 3.8% increase from the year before. The first cause of death was cancer, which also showed an increasing trend (http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012).

The numbers of cancer patients by yearly reported through the Central Cancer Register Office in 2011 showed that the most common cancer was thyroid, followed by breast, colorectal, gastric, lung, liver and cervical cancer. Cervical cancer is the second most common cancer worldwide, of which approximately 500,000 cases have been reported (Kim 2007).

There are several methods of detecting cancer such as a Pap smear, liquid-based cytology, the hybrid capture test, the histopathological test and ultrasound, MRI, nuclear medicine imaging, the use of a tumor marker or a test using serum protein in the blood. In a Pap smear, a speculum was used to visualize the cervix, from which the sample cells were obtained using a brush. The cells were smeared on a glass slide and examined directly. The test was simple and not painful. It was used to detect an early cancer stage (Lee et al. 2007).

In order to solve the limitations of conventional Pap smear, a liquid based test was developed. A separate vial was used to keep the obtained cells and then the cells were smeared evenly on a glass slide using a smear unit after any floating matter was removed. The test was used to examine the cell abnormality. Several clean and intact slides can be produced using the same samples. Being a very accurate test, its application has expanded to the thyroid, brain, spiral cord and bladders (Koh et al. 2007).

A histopathological test refers to a diagnostic confirmation test in which the tissues obtained from surgery or endoscopy was examined first with the naked eyes and then under a microscope. The obtained tissues were thinly sectioned and observed very carefully with the naked eyes to select the area for diagnosis. The selected tissues were processed including fixation and dehydration, it was later sectioned and placed on a slide to be observed via optical microscope. This method was the most frequently used (Hwang et al. 2011).

A tumor marker test detected the products of cancer cells or normal cells affected by cancer cells. Various tests can be used to detect tumor markers in the blood, tissue or excretions and the markers indicate the existence of cancer. This test was used to detect cancers, the characteristics of the cancer cells, remaining cancer cells after a surgery and relapse. A serum protein test was also used to detect cancer using a spoonful of blood. The test instrument has cilia coated with antibodies that selectively bind to cancer cells, not normal cells. When the blood of the patient was dropped onto this unit, the cancer cells bound to the antibodies were detected and the doctor used this result to prepare the prescription for the patient. This test was especially used for breast, prostate gland, colon and lung cancers (http://www.cancer.go.kr/mbs/cancer/subview.jsp?id=cancer_020302000 000).

Ninety-five percent of early detected cervical cancers were treatable. As such, their early detection has been highlighted and various studies have been conducted on this subject. Many studies on the smear unit and the validation of such unit for high-quality slide preparation have been done, as liquid based cytology (LBC) was used to confirm the cytological diagnosis. Choi et al. (2008) prepared a slide of sputum using thinprep instruments for the early detection of lung cancer and validated the test method. Schledermann et al. (2006) validated the condition of the slides to improve the accuracy of diagnosis with LBC. Linder (1998) reported that a thin layer of cells was useful for diagnosis and this new method was seen to become influential enough to replace the conventional Pap smear. Abulafia et al. (2003), De et al. (2013), Jang et al. (2002), Jeon et al. (2004), Lee et al. (2007) and Maksem et al. (2006) proved that LBC was superior to the conventional Pap smear.

The prepared slides were sent to pathologists for cytological diagnosis. As this procedure was manually done, some studies have been conducted to process the cell image, so as to minimize the possible problems. Zhang et al. (2014) conducted a study in which abnormal cervical cancer cells were segmented. Kuan et al. (2012) also performed a study in which cells on the cervix were segmented using a GVF snake algorithm. Hussin et al. (2012) conducted a study on an algorithm that enabled effective analysis by removing the background image. Prasad et al. (2012) performed a study on an edge curvature that detects oval objects. Harndi et al. (2010) conducted a study on the image processing algorithm for effective diagnosis using a Pap smear image. Various studies with different angles on cervix cells have been done.

However, most previous studies were limited to image processing and no study has been conducted yet on cytological diagnosis based on the results of a diagnosis software program. A software program for effective cytological diagnosis was needed to make early cancer detection possible.

MATERIALS AND METHODS

IMPLEMENTATION OF LBC APPLICATION PROGRAM

A GUI-based liquid cell diagnosis program was developed for using the cell imaging process and the diagnosis algorithms was developed in the previous study. Using the guide formulas provided by Matlab, a GUI-based program was developed (Figure 1). The process is as follows:

In a GUI program, each formula was inserted into each components of the callback formula to call the relevant M-file (formula) when the component was operated by clicking the GUI button (Jeong & Baek 2008).

When you start the program, choose image of the cell that was being diagnosed. Then, the selected image was extracted and the calculated area of nucleus cell image was materialized on Figure 3 (Hough transform extraction algorithm) by pushing the image processing button. Through the calculated value, it printed the diagnosis value below the image by diagnosis standard. It can recognize rate of ASCUS, LSIL and HSIL on how many were taken on cell as shown on Figure 2.

Use the editbox to enter the patient's name, age, sex and inspection. Enter the contents of the comment, press the confirm button and the data will be stored. Axes of the six were constructed so as to display an image processed with the original data in the cell image.

The axes of each, with a push button, implemented two buttons of processing and image open. It was also implemented a close button to close the window and save button to save the file that shows the diagnosis has been completed.

IMAGE PROCESSING BY THE HOUGH TRANSFORM EXTRACTION ALGORITHM

The process of cell nucleus area extraction of uterine cervical pap-smears was suggested in this thesis as shown on Figure 3.

In order to deduce an accurate image of target cell that was intended to be implemented in this study, preprocessing of color image was required. For color image processing, RGB image was applied to (1) (Chen et al. 2010).

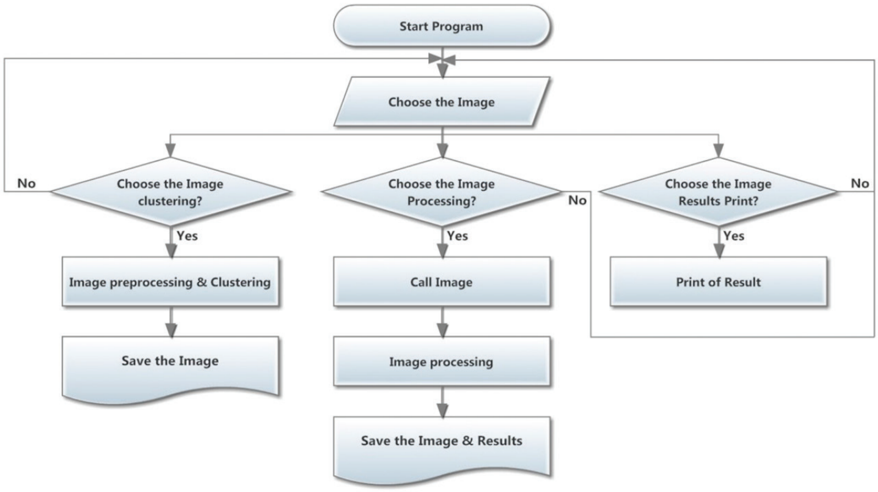


FIGURE 1. Diagnosis algorithm flowchart of the area of the cell nucleus

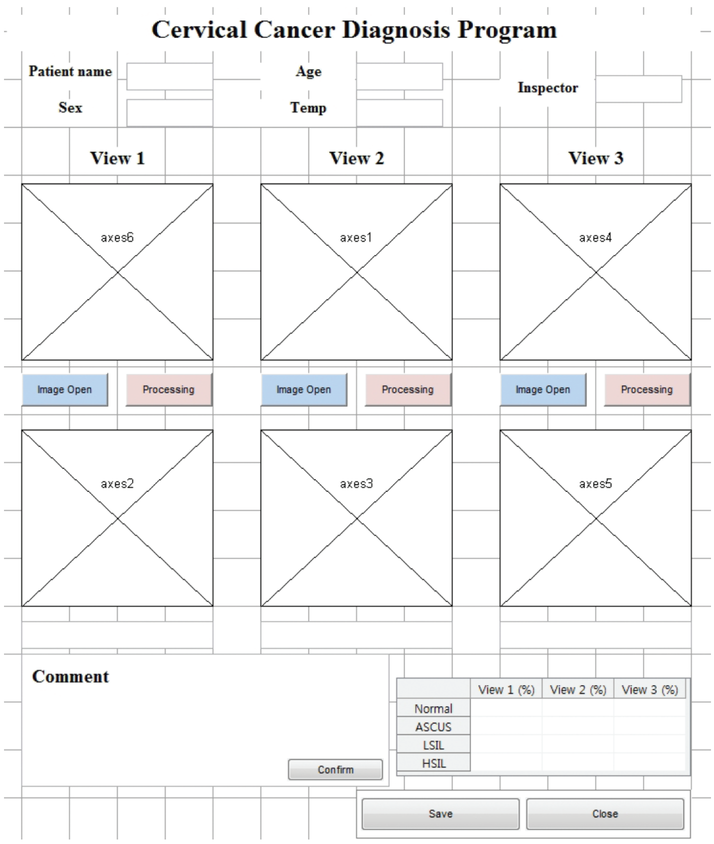


FIGURE 2. Structure of LBC program

$$S = 1 - \frac{3}{(R+G+B)}\left[\min(R,G,B)\right]. \quad (1)$$

First of all, the obtained image was converted to grey image by using (2) and (3) (Mat-Isa et al. 2008).

$$\bar{A} = \frac{\sum_{i=1}^{n} g\left(p_i(x,y)\right)}{n}. \quad (2)$$

Calculate the mean of grey level, Ā (which is known as region mean) and the standard deviation, σ for N × N neighborhood.

$$\sigma = \sqrt{\frac{\sum \left(g\left(p_i(x,y)\right) - A\right)^2}{n-1}}, \quad (3)$$

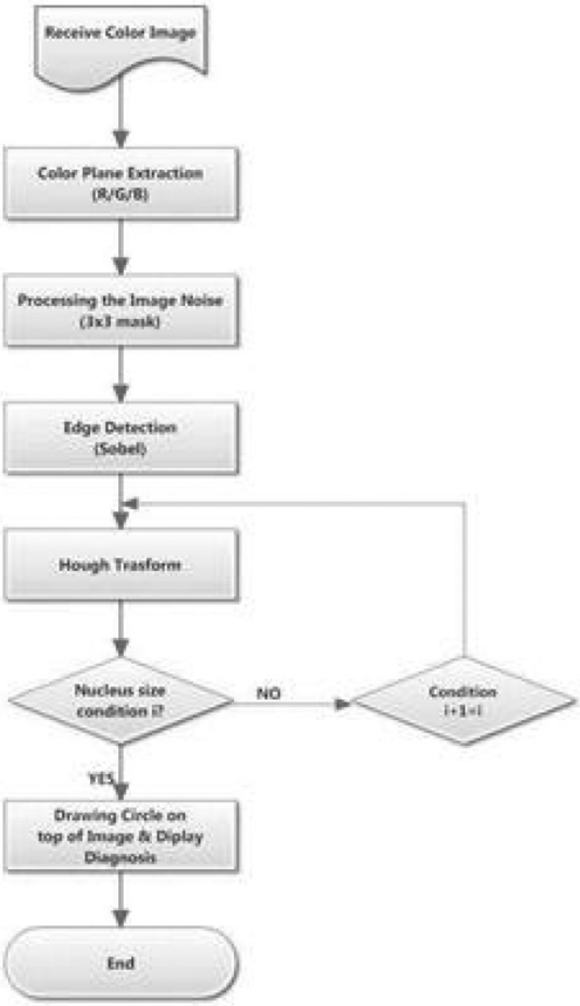


FIGURE. 3. Block diagram of nucleus extraction process

where g (pi(x, y)) is grey level value for I th pixel; n is the total number of pixels in the image; and I programmed the convolution functional in spatial coordinates using (4).

$$h[x,y] = \sum_{i=-\infty}^{\infty} \sum_{j=-\infty}^{\infty} f[x,y]\, g[k-x, l-y]. \quad (4)$$

Noise of converted image was removed by using 2-dimensional Gaussian smoothing filter.

$$[x,y] = \frac{1}{\left(\sqrt{2\pi\sigma}\right)^2} . e^{\frac{x^2+y^2}{2\sigma^2}} . \quad (5)$$

Next, use Sobel edge detection using (6).

$$|\nabla f| = [x,y] = \sqrt{(x_1, y_1)^2 + (x_2, y_2)^2} = \sqrt{(\frac{\partial f}{\partial x})^2 + (\frac{\partial f}{\partial y})^2}, \quad (6)$$

where x1, y1 were vertical mask and x2, y2 were horizontal mask. The edge part of cell image of which noise was removed was detected by using sobel edge detection. Sobel edge detection was masked by dividing it into X axis and Y axis as shown in Figure 4.

1	2	1
0	0	0
−1	−2	−1

−1	0	1
−2	0	2
−1	0	1

FIGURE 4. 3×3 mask used for processing the edge detection by using sobel

The extraction of uterine cervical cell area was done using the Hough transform. The area of nucleus that was detected through edge detection that was a preprocessing stage of cell image was established depending on cell nucleus size based on progress of uterine cervical cancer. Hough transform was used for extracting patterns extended across the whole image region. When it comes to nuclear detection, the area edge line was painted red.

IMPLEMENTATION OF LBC DIAGNOSIS ALGORITHM

The images used in this study were in 600×400 resolution and true color. These images were used to calculate the nucleus area in the cervix epithelial cells. These data were processed as shown in Figure 5.

The pre-processing of the image converted the image into grey scale. In order to remove the noise, applied the mask of 3×3 as shown in Figure 6.

Algorithm being dominantly used among algorithms that extract cell area includes cell area extraction by using ROI (region of interest) (Joo et al. 2004), watershed algorithm using image pixel (Bumford 2003) and Hough transform (Chung et al. 2010; Jiang 2012; Li et al. 2012; Lin & Yu 2011). In this study, the extraction of uterine cervical cell area was done using the Hough transform. A total of 30 cell images were used for cell area extraction. The area condition of nucleus that was detected through the edge detection was a preprocessing stage of cell image (Table 1) depending on the cell nucleus size based on the progress of uterine cervical cancer.

In order to detect the cell corresponding to the condition, cell boundary was calculated in advance. In order to detect target cell in boundary of calculated cell, Hough transform was used. Hough transform was used for extracting patterns extended across the whole image region. This algorithm could be expressed as parameter space (ρ, θ) in straight line that passes point (x_k, y_k) of spatial region as shown in (7).

$$\rho = x \cos\theta + y \sin\theta, \quad (7)$$

ρ is a perpendicular line from the starting point to the line that passes the point (x_k, y_k) as shown on Figure 7(a) and θ is an angle between the perpendicular line and X axis. In addition, Hough transform accumulates (ρ, θ) space by mapping all the points of the (x,y) space into (ρ, θ) space.

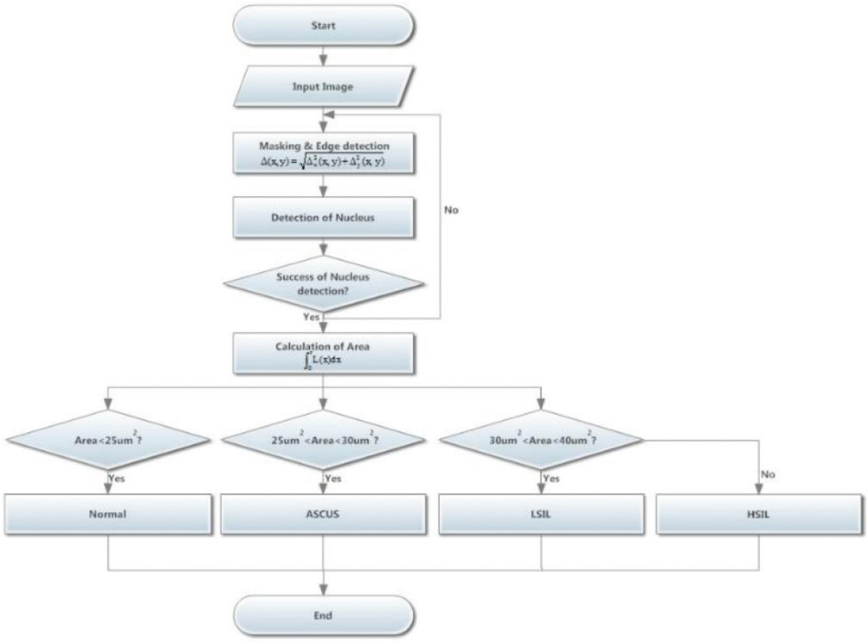


FIGURE 5. Diagnosis algorithm flowchart of the area of the cell nucleus

−1	−1	−1
−1	10	−1
−1	−1	−1

(a)

1	2	1
0	0	0
−1	−2	−1

(b)

−1	0	1
−1	0	2
−1	0	1

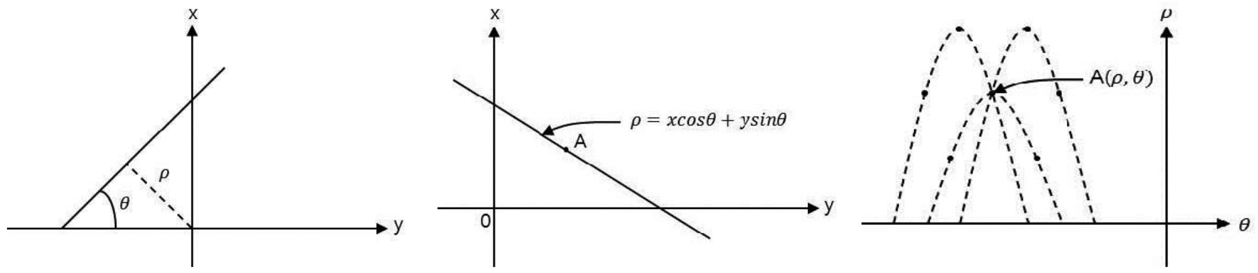
−1	−2	−1
0	0	0
1	2	1

(c)

FIGURE 6. Mask of 3×3 for the processing of the image noise, (a) JVA filter, (b) sobel edge mask and (c) noise mask

TABLE 1. Condition of cell nucleus size based on progress of uterine cervical cancer (Hoda & Hoda 2006)

Condition	Cell nucleus size[μ^2]	Diagnosis
1	15 ~ 25	Normal
2	25 ~ 30	ASCUS
3	30 ~ 38	LSIL
4	38 ~ 45	HSIL



(a) (b) (c)

FIGURE 7. Representation in hough space (ρ,θ) for point(x,y)

In Figure 7(b), point (x_k, y_k) and point (x_k, y_k) draw sine curve in (ρ, θ) space as shown on Figure 7(c) and pass the same point (A) (Bracamontes et al. 2012).

In this algorithm, accumulated point (A) region was made to detect nucleus by one circle being presented by each condition. In order to indicate the point corresponding to target cell as a circle, relevant region was made to be drawn as a circle using (8),

$$(x - a)^2 + (y - b)^2 = r^2. \tag{8}$$

For condition setting, cytological diagnosis standard was established and this standard was based on Bethesda system that was most frequently used in cellular pathology and it was made to indicate that the cell progress condition by detecting target cells corresponding to each condition.

Calculate the mean of grey level, Ā (which is known as region mean) and the standard deviation, σ for N × N neighborhood using (3).

The edge was then detected using (9). The area of detected nucleus was calculated by means of drawing the nucleus where the edge was detected by Hough transform.

$$\Delta(x, y) = \sqrt{\Delta_x^2(x, y) + \Delta_y^2(x, y)}. \tag{9}$$

Subsequently the radius of the area was measured using Hough transform. The radius was under the assumption that the shape being handled was a circle. Then calculate the value of r, which was also used to calculate the area to find a matching nucleus by using (10).

$$\int_0^r L(x)\, dx. \tag{10}$$

If nucleus area was less than 25 μm^2, it was recognized as normal and view the segment. Use the linspace to generate a vector, save to THETA which was a variable value of the angle, nucleus. Meanwhile RHO variable define the function of the matrix of ones and implemented the diameter of the nucleus which was to be allocated by multiplying the size of a one-dimensional array same as (11).

$$\frac{dy}{dx} = \tan\left[\phi(x) - \frac{\pi}{2}\right]. \tag{11}$$

Rotation affects the gradient direction. So, (11) can be rewritten as (12).

$$\frac{dy}{dx} = \tan\left[\phi(x) - \theta - \frac{\pi}{2}\right], \tag{12}$$

where, Φ(x) is the gradient direction; and θ is the angle of rotation. The process of ASCUS, LSIL and HSIL was also applied in the same way. In the case of more than 25 μm^2 less than 30 μm^2, the area of the nucleus was recognized by the ASCUS. In the case of more than 30 μm^2 less than 40 μm^2 was recognized as LSIL. In other cases, it was recognized as HSIL.

RESULTS AND DISCUSSION

IMPLEMENTATION OF LBC PROGRAM RESULTS

This study was designed to develop a GUI-based LBC diagnosis program using the cell imaging process and the diagnosis algorithms. The imaging process and the diagnosis algorithms were easily checked using each button.

Event is executed in the UI control. If you click on the button of each, it can be performed using a callback function to be able to load and execute code that was assigned to the button. Each button was treated as an event, because an error may appear when the button was click continuously; use the event queue to reduce errors.

The GUI application has an advantage that it can use the dialog box to control the flow of the program. Therefore, in this study by using the built-in dialog box, one should be able to check the status. In the bottom section was a comment window for any remarks from the pathologists and it was possible to check the number of abnormal cells in the image through the table at the bottom (Figure 8).

EVALUATION OF LBC PROGRAM

By using the GUI of MATLAB, the implementation of liquid based cytology program were evaluated for this. The results were evaluated as shown in Table 2.

The evaluation results of the diagnosis showed that the accuracy when using liquid based cytology program is

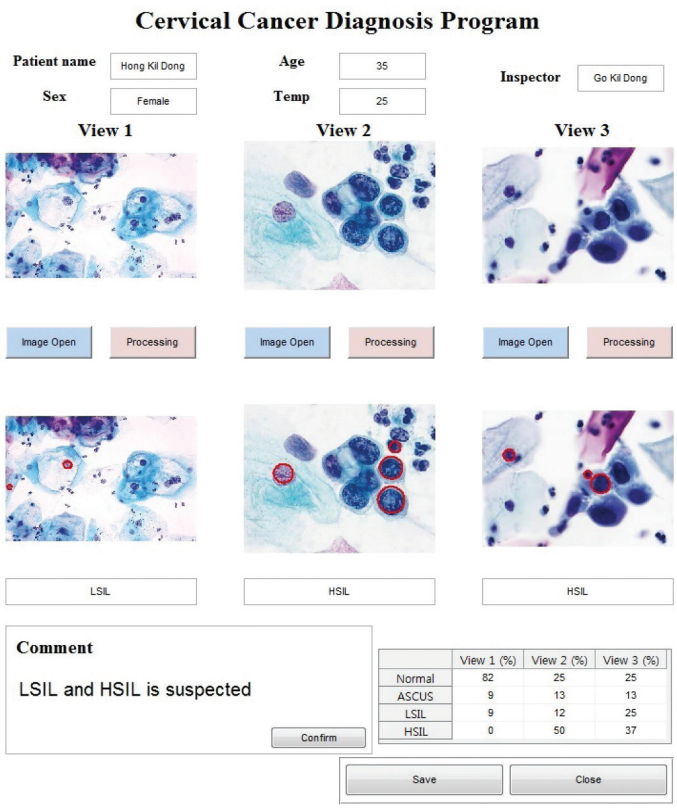


FIGURE 8. Results of LBC program

TABLE 2. Evaluation of the implementation results of LBC program

Cell	Number of slides	Diagnostic slides	Accuracy of detecting(%)
Normal	20	20	100.0
ASCUS	5	5	100.0
LSIL	3	2	66.0
HSIL	2	2	100.0
Average			91.5

91.5%. In LSIL, an error has occurred in one of the slide. The reason of error was determined by the overlapped between cells. Also, as it was developed as Beta version, it needed extra verifications.

EVALUATION OF IMAGE PROCESSING

The evaluation results of the image processing using the Hough transform extraction algorithm software was 95%. There were differences in the accuracy of each program (Table 3).

It was determined that the Hough transform extraction algorithm may be advantageous for imaging than extraction algorithm shown in Table 4.

The extraction happen as a shape of circle, therefore, it needs variable way of approach. The extraction time is almost the same as extraction algorithm took 1.5 s and Hough transform extraction algorithm took 1.3 s. But it has difference on accuracy. The extraction algorithm arbitrarily discolors the nucleus and cytoplasm to separate efficiently, but, detail the extraction was hard to make. Hough transform extraction algorithm were able to extract the nucleus which was important for diagnosis, economically, however, it extract the nucleus in circle which needs variable way of approach.

Thus, in liquid based cytology image processing, it was possible to verify that the image processing using Hough transform extraction algorithm was appropriate.

EVALUATION OF LBC DIAGNOSIS ALGORITHM

Implement the diagnosis algorithms were evaluated for this. The results were evaluated as shown in Table 5.

For the purposes of this study, we needed only one cell to provide a diagnosis. Therefore the images of peripheral cells which could also be important to give a diagnosis in a separate place would make it easier for the technician to use other images than the target cells.

TABLE 3. Evaluation of the image processing algorithm

Cell	Number of slides	Diagnostic slides	Accuracy of detecting(%)
Normal	22	21	95
ASCUS	5	5	100.0
LSIL	6	5	83
HSIL	1	1	100.0
Average			95

TABLE 4. Comparison of extraction algorithm and implementation of image processing algorithm

	Extraction algorithm	Implementation of image processing algorithm
Extraction time (s)	1.5	1.3
Diagnosis accuracy (%)	83	95
Advantage	Efficient separate of cytoplasm and nucleus	Efficient extraction of nucleus which is important part for diagnosis
Weakness	It is hard to have detail extraction and need to approach in variable way	Extraction will happen as shape of circle, so, it needs variable way to approach

TABLE 5. Evaluation of the diagnosis algorithm

Cell	Number of slides	Diagnostic slides	Accuracy of detecting(%)
Normal	20	20	100
ASCUS	5	4	80
LSIL	3	2	67
HSIL	2	2	100.0
Average			87

CONCLUSION

A technique of detecting target cell through cell image processing of LBC examination was implemented. For preprocessing and cytological diagnosis of obtained image, cytological diagnosis result corresponding to each condition was deduced through Hough transform for detecting the target cell by extraction algorithm and Hough transform extraction algorithm. It will be succeeded depending on the pixel value to convert the color of the cytoplasm and cell nucleus by extraction algorithm. But, it was determined that there was a need to resolve the issues that were nested between cells.

We used the LBC method to automate the diagnosis works for the cervical cells. Since it was indicated in a color image, the process becomes more efficient since cytotechnologist can give a quicker diagnosis.

As a result of diagnosis algorithm, the development of the cells resulted in varied nuclei sizes. It was also discovered that the area could be helpful in making diagnosis. In doing so it was more than likely that other cells could be missed. In some cells, ASCUS cells were diagnosed as LSIL cells or LSIL cells were diagnosed as ASCUS cells. The causes of the diagnosis failure were because there was no difference in the nucleus size.

The early detection of cervical cancer has decreased patient mortality. LBC application program was conducted to develop and validate a GUI-based cell diagnosis program for quicker and easier diagnosis.

A software program was developed by combining the results of previous studies on the imaging process with those of the diagnosis program. This study confirmed that such program makes cytological diagnosis very simple. However, this program is still in its beta version and has not yet been optimized. For its optimization, repeated operation was required. Also, the suitability of this program should be tested to allow its use in the LBC market. Also, continuous studies must be done to come up with a special program for cervical cancer diagnosis.

The results of this study showed that the automation of liquid cytology can provide the efficiency of diagnosis and presents new paradigm cytology. Therefore, the cytological automatic diagnosis system was possible to provide efficacy for early diagnosis of cancer.

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Seong-Hyun Kim & Dong-Wook Kim*
Division of Biomedical Engineering
Chonbuk National University
567 Baekje-daero, Deokjin-gu
Jeonju-si, Jeonbuk
South Korea

Han-Yeong Oh
Department of Healthcare Engineering
Chonbuk National University
567 Baekje-daero, Deokjin-gu
Jeonju-si, Jeonbuk
South Korea

Dong-Wook Kim*
Research Center of Healthcare & Welfare Instrument for the Aged
Chonbuk National University
567 Baekje-daero, Deokjin-gu
Jeonju-si, Jeonbuk
South Korea

*Corresponding author; email: biomed@jbnu.ac.kr

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