COMPUTER-AIDED SCREENING SYSTEM FOR CERVICAL PRECANCEROUS CELLS BASED ON FIELD EMISSION SCANNING ELECTRON MICROSCOPY AND ENERGY DISPERSIVE X-RAY

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

FACULTY OF ENGINEERING
UNIVERSITY OF MALAYA
KUALA LUMPUR

2016

UNIVERSITI MALAYA

ORIGINAL LITERARY WORK DECLARATION

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Registration/Matric No**: KHA120092**

Name of Degree**: PhD of Engineering**

Title of Project Paper/Research Report/Dissertation/Thesis ("this Work")**:**

Computer-aided screening system for cervical precancerous cells based on Field emission scanning electron microscopy and energy dispersive x-ray

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PREFACE

Six chapters of this thesis (Chapter 2-7) comprised the manuscripts which include the body of the work accepted/submitted for publication in ISI-indexed journals.

Chapter 2 contains literature review reprinted text from The Scientific World Journal, Jusman, et al., Intelligent Screening Systems for Cervical Cancer, pp.1-15.

Chapter 3 contains reprinted text from The Scientific World Journal, Jusman, et al., Investigation of CPD and HMDS Sample Preparation Techniques for Cervical Cells in Developing Computer-Aided Screening System Based on FE-SEM/EDX, pp.1-11.

Chapter 4 contains reprinted text submitted to Journal of Biomedical Optics, Jusman, et al., A Protocol for Enhanced Imaging and Quantification of Cervical Cells under Scanning Electron Microscope.

Chapter 5 contains reprinted text submitted to Journal of Innovative Optical Health Sciences, Jusman, et al., Topographic Structure and Element Properties of Cervical Cancer under Field Emission Scanning Electron Microscope and Energy Dispersive X-ray: Features and Investigation.

Chapter 6 contains reprinted text from to Journal of Innovative Optical Health Sciences, Jusman, et al., A system for detection of cervical precancerous in Field Emission Scanning Electron Microscope Images using texture features, vol. 10, No. 2, pp.1-12.

Chapter 7 contains reprinted text (accepted) to Optical Engineering, Jusman, et al., A Computer-Aided for Cervical Precancerous Cells Screening System based on FE-SEM/EDX Image and Spectra.

ABSTRACT

Cervical cancer has caused many deaths each year. Screening tests, such as Papanicolou (Pap) smears and Liquid based Cytology (LBC) for detection of precancerous change, are able to avoid the occurrence of cervical cancer. However, these tests still have disadvantages such as being inaccurate due to human errors (the false negative rate reaching 50%) and long processing time due to manual method of determining cell abnormality based on morphological signs by the pathologists. Several researchers have developed computer systems for analysis of Pap smear and LBC images. However, the systems are still not satisfactory as they only use morphological features. Currently, Field Emission Scanning Electron Microscopy and Energy Dispersive X-Ray (FE-SEM/EDX) has great capability to extract qualitative and quantitative data from all types of materials simultaneously. Based on this capability, this study proposed FE-SEM/EDX as a data acquisition technique to develop computer-aided screening system for cervical precancerous cells. The developed system consists of data acquisition, features extraction, and classification stages. Before the data acquisition stage, sample preparations were investigated to obtain qualitative and quantitative data from FE-SEM/EDX. Hexamethyldisilazane (HMDS) and Critical-Point Drying (CPD) sample preparation techniques were compared in term of the quality of the FE-SEM image, quantification of elements distribution, and rapidity of processing time. The HMDS sample preparation technique has better results than the CPD technique for the terms. For data acquisition, FE-SEM/EDX was implemented at specific working distance (10 mm) for an average voltage range (5 to 20 kV), performed under low vacuum condition. FE-SEM image and elemental distributions (FE-SEM/EDX data) of the samples were obtained simultaneously. In the feature extraction stage, cervical precancerous features were extracted from the FE-SEM/EDX data. Proposed image processing techniques and signal analyses were applied to the FE-SEM/EDX data for feature extraction. Finally,

for the classification stage, the Discriminant Analysis (DA) concept was used to classify the cervical precancerous cells based on the Bethesda system (i.e. normal, Low-grade Squamous Intraepithelial Lesion (LSIL) and High-grade Squamous Intraepithelial Lesion (HSIL)). The results indicated that eliminating the osmium HMDS technique from the sample preparation technique was favorable as it resulted in improved quality for sample preparation in term of quality of FE-SEM image and quantification of elements distribution results in data acquisition, and rapid processing time in sample preparation. In the feature extraction stage, FE-SEM/EDX images provided statistical features information based on pixel intensities, namely contrast, homogeneity, entropy and energy. Furthermore, the FE-SEM/EDX spectra can also provide information on the ratio of the peaks and the ratio of the corrected area under the peaks. The extracted features were combined into datasets for further processing using DA for classification. Our system achieved accuracy, sensitivity, and specificity results of 98.9%, 98.8%, and 99.1%, respectively. The results indicate that the chosen sample preparation method and the usage of FE-SEM/EDX for data acquisition, feature extraction, and classification techniques achieved good performances for developing a computer-aided screening system. Therefore, a computer-aided screening system for cervical precancerous cells has been successfully developed in this study.

ABSTRAK

Kanser pangkal rahim telah menyebabkan banyak kematian setiap tahun. Ujian saringan, seperti ujian palitan Papanicolou (Pap) dan sitologi berasaskan cecair (LBC) yang digunakan untuk mengesan peringkat kanser, dapat mengelakkan berlakunya kanser pangkal rahim. Walau bagaimanapun, ujian saringan masih mempunyai kelemahan seperti ketidaktepatan disebabkan oleh kesilapan manusia (dengan kadar salah negatif mencapai 50%) dan masa pemprosesan yang lama kerana pakar patologi itu menggunakan tanda-tanda morfologi keabnormalan sahaja secara manual. Beberapa penyelidik telah mengembangkan sistem komputer untuk analisis imej palitan Pap dan imej LBC. Walau bagaimanapun, sistem masih tidak memuaskan kerana menggunakan ciri-ciri morfologi sahaja. Pada masa kini, bidang mikroskopi electron imbasan pelepasan medan dan X-ray tenaga serakan (FE-SEM/EDX) mempunyai keupayaan yang hebat untuk mengekstrak data kualitatif dan kuantitatif daripada semua jenis bahan secara serentak. Berdasarkan keupayaan tersebut, kajian ini mencadangkan FE-SEM/EDX sebagai teknik perolehan data bagi membangunkan sistem saringan bantuan komputer untuk sel-sel pra-kanser pangkal rahim. Sistem yang dikembangkan terdiri daripada peringkat perolehan data, pengektrakan ciri-ciri, dan klasifikasi. Sebelum peringkat perolehan data, penyediaan sampel disiasat untuk mendapatkan data kualitatif dan kuantitatif dari FE-SEM/EDX. Teknik penyediaan sampel Hexamethyldisilazane (HMDS) dan kritikal titik pengeringan (CPD) dibandingkan dari segi kualiti imej FE-SEM, kuantifikasi pengedaran elemen, dan masa pemprosesan yang cepat. Teknik penyediaan sampel HMDS mempunyai keputusan yang lebih baik daripada teknik CPD dalam setiap segi. Bagi perolehan data, FE-SEM/EDX digunakan pada jarak kerja tertentu (10 mm) bagi julat voltan purata (5 hingga 20 kV) dan dilakukan di bawah keadaan vakum rendah. Imej FE-SEM dan taburan unsur daripada sampel (data FE-SEM/EDX) diperolehi secara serentak. Di peringkat pengekstrakan ciri, ciri-ciri pra-

kanser pangkal rahim diekstrak daripada data FE-SEM/EDX. Teknik pemprosesan imej yang dicadangkan dan isyarat analisis digunakan untuk teknik pengekstrakan ciri daripada data FE-SEM / EDX. Akhir sekali, bagi peringkat klasifikasi, konsep Analisis Pembezaan (DA) digunakan untuk mengklasifikasikan sel-sel pra-kanser pangkal rahim berdasarkan sistem Bethesda (iaitu normal, Luka intraepithelial skuamus gred rendah (LSIL) dan Luka intraepithelial skuamus gred tinggi (HSIL)). Keputusan menunjukkan bahawa teknik tiada Osmium HMDS dipilih sebagai keputusan yang lebih baik untuk penyediaan sampel dari segi kualiti imej FE-SEM dan kuantifikasi taburan unsur-unsur dalam keputusan perolehan data, dan masa pemprosesan yang cepat dalam penyediaan sampel. Di peringkat pengekstrakan ciri-ciri, imej FE-SEM/EDX memberikan ciri-ciri maklumat statistik berdasarkan intensiti piksel, iaitu kontras, kehomogenan, entropi dan tenaga. Tambahan pula, spektrum FE-SEM/EDX boleh memberikan maklumat mengenai nisbah puncak dan nisbah kawasan yang dibetulkan di bawah puncak. Ciri-ciri yang diekstrak digabungkan kedalam set data yang akan dimasukkan kedalam DA untuk klasifikasi. Sistem kami mencapai keputusan ketepatan, kepekaan, dan kekhususan; 98.9%, 98.8%, dan 99.1% masing-masing. Keputusan menunjukkan bahawa kaedah penyediaan sampel yang dipilih dan penggunaan FE-SEM/EDX untuk perolehan data, teknik pengekstrakan ciri dan klasifikasi mencapai prestasi yang baik untuk mengembangkan sistem saringan bantuan komputer. Oleh itu, sistem pemeriksaan bantuan komputer untuk sel-sel pra-kanser pangkal rahim telah berjaya dikembangkan dalam kajian ini.

ACKNOWLEDGMENT

In the name of Allah, the most compassionate, the most merciful.

I would like to express my gratitude to the following people and organization for their help and valuable contribution to the completion of this thesis.

First and foremost, I would like to thank to Dr. Ng Siew Cheok and Prof. Ir. Dr. Noor Azuan Abu Osman for their invaluable supervisory support and guidance during the duration of this study. I would especially like to thank to Dr. Teoh Kean Hooi from Department of Pathology, Faculty of Medicine, University of Malaya for all the hours of his insightful advice and technical support in sample collection.

I am greatly indebted to the University of Malaya for its financial support under the High Impact Research (HIR), grant No: D000014-16001. I would like to thank to technicians in Field Emission Scanning Electron Microscopy (FE-SEM) laboratory, and in laboratory at Research Management Centre (RMC) for friendly conservation and insightful advice during sample preparation and data acquisition in this study.

Most importantly, I'd like to thank my wonderful husband, Ahmad Zaki, for his constant love, for motivating me in loving and caring ways, for supporting and helping me in this study, and for the happiness he has brought into my life in terms of his patience and cooperativeness to take care of our children Fatin Sahira Ahmad, Firas Faiq Ahmad, and Filzah Delisha Ahmad during our Phd Journey. My special acknowledgments for my beloved mother Jusnelli, brothers Mico Anggara and M. Yogy Prasetya, and sister Iffatuz Zahra for their love and hope which encourage me all along without hesitation. Finally, I would like to express my greatest appreciation to my PhD journey friends in Forum Ukhuwah Studi Islam (FUSI) in UM (especially Mbak Ira Puspita Sari, Teh Fitriani, Arniza Fitri, Mirta Widia, and Farah Ramadhani) and thanks to valuable supports from my halaqoh members.

DEDICATION PAGE

To my **mother** and (**late) father** whose love is the eternal motive of my life

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LIST OF ABBREVIATIONS

MRI	: Magnetic Resonance Imaging
X-ray CT	: X-ray Computed Tomography
HPV	: Human Papillomavirus
CIN	: Cervical Intraepithelial Neoplasia
LSIL	: Low-grade Squamous Intraepithelial Lesion
HSIL	: High-grade Squamous Intraepithelial Lesion
Pap	: Papanicolou
LBC	: Liquid Based Cytology
DCCC	: Development Conference of Cancer of the Cervix
US-NIH	: United State National Institute of Health
FDA	: Food and Drug Administration
IAC	: International Academy of Cytology
WHO	: World Health Organization
ATR	: Attenuated Total Reflection
FTIR	: Fourier Transform Infrared
FE-SEM	: Field Emission Scanning Electron Microscopy
EDX	: Energy Dispersive X-ray
DNA	: Deoxyribonucleic Acid
VILI	: Visual Inspection after applying Lugol's iodine
VIA	: Visual Inspection after applying Acetic Acid
HSDI	: Hyperspectral Diagnostic Imaging
EMS	: Electromagnetic Spectroscopies
FISH	: Fluorescent in Situ Hybridization
ANN	: Artificial Neural Network

SVM : Support Vector Machine

KNN : K-Nearest Neighbor

LDA : Linear Discriminant Analysis

LR : Logistic Regression

DT : Decision Tree

SG : Savitzky-Golay

AW : Aceto White

TZ : Transformation Zone

ROI : Region of Interest

ROSE : Rotating Structuring Element

SE : Squamous Epithelium

SR : Specular Reflection

CC : Cervical Canal

KMC : K–Means Clustering

CPD : Critical-Point Drying

HMDS : Hexamethyldisilazane

PBS : Phosphate-Buffered Saline

FEG : Field Emission Gun

3-D : Three Dimensional

UMMC : University of Malaya Medical Center

MEC : Medical Ethics Committee

I-L : In-Lens

E-T : Everhart-Thornley

DA : Discriminant Analysis

ITMO : Intensity Transformation and Morphological Operation

TP : True Positive

TN : True Negative

FP : False Positive

FN : False Negative

ISCFE : Image and Spectra Cervical Cells Features Extraction

LIST OF SYMBOLS

%	: Percentage
cm^{-1}	: Per centimeter
nm	: Nanometer
μm	: Micrometer
kV	: Kilo Volt
s	: Second
^{0}C	: Degree Celsius
mm	: Millimeter
h	: Hour
ml	: Milliliter
C	: Carbon
N	: Nitrogen
O	: Oxygen
Na	: Sodium
Mg	: Magnesium
Ca	: Calcium
Cu	: Copper
Al	: Aluminum
Si	: Silicon
Y	: Yttrium
Zn	: Zinc
Cl	: Chlorine
Fe	: Iron
K	: Potassium
Ti	: Titanium
Au	: Gold