RADIOMICS ANALYSIS AND SUPERVISED MACHINE LEARNING MODEL FOR CLASSIFICATION OF CERVICAL CANCER IMAGES USING DIFFUSION WEIGHTED IMAGING-MRI

By

ZARINA BINTI RAMLI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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DEDICATION

I dedicated this thesis to my esteemed husband & my soulmate, Mohd Rahimi B. Ab Rahman, my lovely parents Normah Binti Sidek & my mother-in-law Saadah Binti Yusoff, my kids Raisha Qistina, Muhammad Raqyal and Muhammad Rizqin for their unwavering support and motivation throughout this academic journey.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman : Associate Professor Muhammad Khalis bin Abdul Karim, PhD
Faculty : Science

Cervical cancer is the third most prevalent cause of mortality among women in Malaysia. Early detection, especially in high-risk populations, can reduce mortality rates and enable timely treatment. This study investigates the efficacy of staging classification using diffusion-weighted imaging magnetic resonance imaging (DWI-MRI) through radiomic analysis and machine learning. Data were retrospectively analyzed from the picture archiving and communication system (PACS) at Institut Kanser Negara (IKN) in Putrajaya, Malaysia. The first objective involved 30 patients to evaluate the repeatability and reproducibility of manual and semi-automated segmentation methods on DWI-MRI images. Intra-class correlation coefficient (ICC) analyses were performed on 662 radiomic features encompassing texture, shape, and first-order statistics. The semi-automated active contour model (ACM) algorithm (average ICC = 0.952 ± 0.009, $p > 0.05$) was found to be more robust and reproducible than fully manual segmentation (average ICC = 0.897 ± 0.011, $p > 0.05$). The second objective assessed the stability of radiomic features using contrast-limited adaptive histogram equalization (CLAHE) for image enhancement of 80 DWI-MRI images, enhanced images exhibited improved stability in radiomic features (ICC = 0.990 ± 0.005, $p < 0.05$), outperforming both semi-automated (ICC = 0.864 ± 0.033, $p < 0.05$) and manual methods (ICC = 0.554 ± 0.185, $p > 0.05$). The third objective focused on classifying cervical cancer stages using DWI-MRI radiomic features. A support vector machine (SVM) classifier yielded excellent performance metrics, accuracy of 0.77, and precision of 0.63, with an area under the curve (AUC) of 96%. Additionally, the SVM algorithm was evaluated based on its performance across different DWI b-values, aiming to optimize scanning time. In conclusion, SVM-based models can develop accurate and reproducible software for classifying cervical cancer stages, significantly enhancing the role of radiology by enabling more quantitative MRI interpretations. This study underscores the potential of radiomic analysis to improve the accuracy of medical reports, reduce dependency on contrast agents, and enhance early detection of cervical cancer.

Keywords: Cervical cancer, DWI-MRI, Radiomic analysis, Supervised machine learning.

SDG: GOAL 3: Good Health and Well-Being, GOAL 11: Sustainable Cities and Communities

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ANALISIS RADIOMIK DAN MODEL PEMBELAJARAN MESIN DISELIA BAGI KLASIFIKASI KANSER SERVIKS MENGGGUNAKAN IMEJ PENGIMEJAN WAJARAN RESAPAN - MRI

Oleh

ZARINA BINTI RAMLI

Oktober 2024

Pengerusi : Profesor Madya Muhammad Khalis bin Abdul Karim, PhD
Fakulti : Sains

Kanser serviks adalah punca kematian ketiga paling lazim di kalangan wanita di Malaysia. Pengesanan awal, terutama dalam populasi berisiko tinggi, dapat mengurangkan kadar kematian dan membolehkan rawatan diberikan tepat pada masanya. Kajian ini menilai ketepatan klasifikasi peringkat menggunakan imej pengimejan wajaran resapan pengimejan resonans magnet (DWI-MRI) melalui analisis radiomik dan pembelajaran mesin. Data dianalisis secara retrospektif dari sistem pengarkiban gambar dan komunikasi (PACS) di Institut Kanser Negara (IKN) Putrajaya, Malaysia. Objektif pertama melibatkan 30 pesakit untuk menilai kebolehulangan dan kebolehasilan proses segmentasi manual dan separa automatik pada imej DWI-MRI. Analisis pekali korelasi intra-kelas (ICC) bagi 662 ciri radiomic tekstur, bentuk, dan statistik peringkat pertama. Algoritma model kontur aktif (ACM) bagi separa automatik (purata ICC = 0.952 ± 0.009, $p > 0.05$) didapati lebih teguh dan kebolehhasilan yang tinggi berbanding segmentasi manual (purata ICC = 0.897 ± 0.011, $p > 0.05$). Objektif kedua menilai kestabilan ciri radiomik menggunakan

penyamaan histogram adaptif terhad kontras (CLAHE) untuk 80 imej DWI-MRI, imej yang dipertingkatkan menunjukkan kestabilan yang lebih baik dalam ciri radiomik (ICC = 0.990 ± 0.005, $p < 0.05$) berbanding kaedah separa automatik (ICC = 0.864 ± 0.033, $p < 0.05$) dan manual (ICC = 0.554 ± 0.185, $p > 0.05$). Objektif ketiga memberi tumpuan kepada pengelasan peringkat kanser serviks menggunakan ciri radiomik DWI-MRI. Pengelasan mesin vektor sokongan (SVM) menghasilkan metrix prestasi yang cemerlang, ketepatan 0.77, kejituan 0.63 dengan kawasan di bawah lengkung (AUC) 96%. Di samping itu, algoritma SVM digunakan untuk menilai prestasi merentas nilai b DWI yang berbeza bagi mengoptimumkan masa imbasan. Kesimpulannya, model berasaskan SVM dapat membangunkan perisian yang tepat dan kebolehulangan yang tinggi untuk mengklasifikasikan kanser serviks, serta meningkatkan peranan radiologi melalui pentafsiran imej MRI yang lebih kuantitatif. Kajian ini menekankan potensi analisis radiomik dalam meningkatkan ketepatan laporan perubatan, mengurangkan kebergantungan kepada agen kontras, dan meningkatkan pengesanan awal kanser serviks.

Kata Kunci: Kanser serviks, Pengimejan wajaran resapan-pengimejan resonans magnet. Analisis radiomic, Pembelajaran mesin diselia,

SDG: MATLAMAT 3: Kesihatan Baik dan Kesejahteraan, MATLAMAT 11: Komuniti dan Bandar yang Lestari

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Muhammad Khalis bin Abdul Karim, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Mohd Amiruddin bin Abd Rahman, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Member)

Mohd Saiful Asmal bin Abdul Rani, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 13 January 2025

TABLE OF CONTENTS

			Page
ABSTRACT			i
ABSTRAK			iii
ACKNOWLEDGEMENTS			v
APPROVAL			vi
DECLARATION			viii
LIST OF TABLES			xiii
LIST OF FIGURES			xv
LIST OF ABBREVIATIONS			xviii
CHAPTER			
1	**INTRODUCTION**		1
	1.1	Research background	1
	1.2	Problem statement	3
	1.3	Research objectives	5
	1.4	Scope of study	6
	1.5	Research significance	6
	1.6	Thesis outlines	9
2	**LITERATURE REVIEW**		11
	2.1	Introduction	11
	2.2	Reproductive system	11
		2.2.1 Cervical cancer diseases	13
		2.2.2 Factors contributing to cancer of cervical	15
		2.2.3 Staging in cervical cancer	18
		2.2.4 Screening test of cervical cancer	22
		2.2.5 Imaging technique of cervical cancer	24
	2.3	MRI	26
		2.3.1 History of MRI and installation in Malaysia	26
		2.3.2 Physics of MRI	28
		2.3.3 DWI/ADC MRI parameter	29
		2.3.4 B-value	32
	2.4	Radiomics	35
		2.4.1 History of radiomic	35
		2.4.2 Feature extraction	36
		2.4.3 First order statistics	36
		2.4.4 Second order statistical features analysis	38
		2.4.5 Higher-order statistical features analysis	42
		2.4.6 Shape features analysis	44
	2.5	Image processing	49
	2.6	Image enhancement	49
		2.6.1 Edge enhancement	50
		2.6.2 Adaptive Histogram Equalization (AHE)	51
		2.6.3 Contrast limited adaptive histogram equalization (CLAHE)	51

	2.7	Radiomic image segmentation process	55
		2.7.1 Manual segmentation	55
		2.7.2 Semi auto segmentation	56
		2.7.3 Automatic segmentation	57
	2.8	Machine Learning	59
		2.8.1 Machine learning in cancer classification	59
		2.8.2 Supervised machine learning classifiers	62
		2.8.3 The support vector machine (SVM)	63
		2.8.4 The decision tree (DT)	65
		2.8.5 The logistic regression (LR)	67
		2.8.6 Study gap analysis	68
	2.9	Summary	72
3	**METHODOLOGY**		73
	3.1	Introduction	73
	3.2	Research design	73
	3.3	Data collection process	76
		3.3.1 MRI	76
		3.3.2 3D slicer	78
		3.3.3 Python	79
		3.3.4 Matrix Laboratory (MATLAB)	79
		3.3.5 K-Fold cross validation	80
		3.3.6 Filter normalization algorithm	81
	3.4	Preprocessing data segmentation	83
	3.5	Contrast enhancement and segmentation	88
	3.6	Model classification	92
		3.6.1 SVM algorithm	93
		3.6.2 LR algorithm	95
		3.6.3 DT algorithm	96
	3.7	Performance evaluation DWI b-value	99
	3.8	Statistical evaluation	104
		3.8.1 Intra-class correlation coefficient	104
		3.8.2 Performance matrix evaluation	105
	3.9	Summary	107
4	**RESULTS AND DISCUSSION**		109
	4.1	Introduction	109
	4.2	Stability of reproducibility and repeatability of radiomic features	109
	4.3	Impact of the contrast enhancement in the stability of radiomic features	126
	4.4	Performance evaluation of supervised machine learning classifier	140
	4.5	Comparison performance analysis of support vector machine with different b-value	156
	4.6	Summary	166

5	**CONCLUSION AND RECOMMENDATION**	167
5.1	Conclusion	167
5.2	Limitation and recommendation	169
REFERENCES		171
APPENDICES		187
BIODATA OF STUDENT		197
LIST OF PUBLICATIONS		198

LIST OF TABLES

Table		Page
2.1	Staging classification of cancer based on TNM and FIGO classification of cervical cancer	20
2.2	History of MRI technology progression and development according to years	27
2.3	The description of computational equation of first order statistics features	37
2.4	The description of computational equation of second order statistics features	40
2.5	The description of computational equation of higher order statistics features	43
2.6	The description of computational equation of shape features	45
2.7	Illustrates the utilization of texture and shape features in respective fields	48
2.8	The implementation of CLAHE in different studies.	53
2.9	The various implementation segmentation technique in the field of radiomic features analysis	58
2.10	The influence of different studies on the deployment of classifiers in machine learning classification	61
3.1	Technical specification of Magnetom Verio 3Tesla Siemens in IKN Putrajaya	76
3.2	The patients demographic data including in this study	78
3.3	Scanning parameter of different b-value with the scanning time	99
4.1	86 radiomic characteristics utilizing using a 3D-slicer from volume of interest	111
4.2	The reproducibility between semi-automatic and manual features extracted from the segmentation process	119
4.3	Radiomic feature ICC of inter-observer analysis between manual, semi 1 and semi 2 features	121
4.4	The selection of radiomic features in contrast enhancement	129

4.5	Reproducibility group of features according to segmentation technique and image	132
4.6	Variations in ICC value obtained from selected subject	136
4.7	The 55 features characteristics of texture, first orders statistics and shape order features from the segmentation	141
4.8	31 wavelength features of texture and parameter of wavelet, texture type and texture parameter from the segmentation process	143
4.9	The comparison of performance evaluated with different training data percentages using metrics of accuracy and precision	147
4.10	The outlined of supervised machine learning performance in classifying cervical cancer.	151
4.11	The analysis of machine learning algorithms in predicting cervical cancer staging	154
4.12	Performance metrics for TPOT and conventional machine learning generate pipelines and computational time	156
4.13	The analysis of textural, first order statistics, and shape-based features between b-value 50, 400 and 900	160
4.14	The diagnostic performance of each b-value 50, 400 and 900 according to their performance	163

LIST OF FIGURES

Figure		Page
2.1	Anatomy of female reproductive system show location of main component and organ relationships	13
2.2	The projection of cancer incidence among women in Malaysia indicates that cervical cancer ranks third in terms of prevalence	14
2.3	The projection of cervical cancer incidence in Eastern Asia with Malaysia represents 11.9%	15
2.4	Stages of cervical dysplasia precursor from normal cells progress to cervical cancer	17
2.5	History of MRI machine installed in Malaysia from 1987s until 2018s	27
2.6	Interaction of protons before, during and after application of magnetic field and radiofrequency waves	29
2.7	DWI Region with the most prominent restrictive diffusion (hyperintense signal) on b-value 1000	30
2.8	ADC map show low signal area of locally advanced rectal tumor	31
2.9	Process of texture extraction method from the primary image pixel into gray co matrix histogram	39
2.10	The supervised machine learning classifiers	63
2.11	SVM classification diagram between separating hyperplane of support vector	65
2.12	Classification based on DT flowchart contain of decision node and leaf node construction	66
2.13	The linear regression plot of LR according to dependent and independent variable	67
2.14	The distribution of articles according to country.	69
2.15	World map depicting research efforts focused on radiomic cervical cancer.	70
2.16	The graph of distribution related articles according to years	71
3.1	The overall design of this research workflow with three main processes of radiomic	75

3.2	Tesla Magnetom Verio MRI at Radiology department, IKN Putrajaya	77
3.3	The research workflow for phase I which involved ethical process and data extraction using 3D slicer for segmentation.	82
3.4	The research workflow for phase II which including comparison between manual and semi-auto segmentation	84
3.5	The overall research workflow in stability and reproducibility	86
3.6	The predefined process manual and semi-auto segmentation with level tracing of ACM algorithm	87
3.7	Technique of ACM algorithm segmentation using 3D slicer software in 3 plane of axial, coronal and sagittal	88
3.8	The research workflow for phase III including the image enhancement process of CLAHE	92
3.9	The research workflow for phase v performance classifier of supervised machine learning	98
3.10	Images visualization of b-value 50 parameter in cervical cancer	100
3.11	Images visualization of b-value 400 parameter in cervical cancer	100
3.12	Images visualization of b-value 900 parameter in cervical cancer	101
3.13	The research workflow for phase vi performance classifier of SVM with different b-value	103
3.14	Protocol of 3 b-value Scanning Parameter	104
3.15	Protocol of 2 b-value Scanning Parameter	104
3.16	Confusion matrix calculation for the prediction and model performance evaluation	106
4.1	Comparisons of shape-based feature values for the intra-class correlation coefficient (ICC)	114
4.2	Intra-class correlation coefficient (ICC) comparisons for textural features	115
4.3	Intra-class correlation coefficient (ICC) value comparisons for first order statistical characteristics	116
4.4	Correlation heatmap between observer characteristics in semi-automatic and manual segmentation features	117

4.5	The boxplot of the ICC value reflects the repeatability of radiomic properties across observers	120
4.6	Process of manual segmentation tumour on DWI-MRI images in the orientation of axial plane	127
4.7	Process of image enhancement DWI-MRI images	128
4.8	Process image enhancement semi-automated segmentation with CLAHE	128
4.9	Systematic flow of manual, semi-automated, and CLAHE between 4 independent observer and 2 observer for ICC process	130
4.10	The comparison of the ICC between segmentation for first order histogram-based features in manual, semi-automated and CLAHE	133
4.11	Comparison of the ICC value between segmentation for shape-based features in manual, semi-automated and CLAHE	133
4.12	Comparison of the ICC value for the textural features in manual, semi-automated and CLAHE	134
4.13	Comparison of selected ICC value among in different observers between manual, semi auto and CLAHE	138
4.14	Heatmap matrix illustrating the relationships between different stage features of groups 1 and groups 2	144
4.15	The heatmap confusion matrix for SVM classifier	148
4.16	The heatmap confusion matrix for LR classifier	148
4.17	The heatmap confusion matrix for DT classifier	149
4.18	Displays the ROC curves for SVM, LR, and DT models with the area of ROC characteristic	151
4.19	Distribution analysis of textural, first order statistics, and shape-based features between b-value 50, 400 and 900	161
4.20	Displays the ROC curves for b-value 50, 400 and 900 using SVM with the ROC graph	163
4.21	The comparison of scanning time between 3 b-value and 2 b-value of scanning protocol DWI-MRI	165
5.1	Overall research summary of the thesis with the findings and summary from each chapter	170

LIST OF ABBREVIATIONS

Acc	Accuracy
ACM	Active contour models
ADC	Apparent diffusion coefficient
AI	Artificial intelligence
ANN	Artificial neural networks
ANOVA	Analysis of variance
AUC	Area under the curve
CLAHE	Contrast limited adaptive histogram equalization
CNN	Convolutional neural network
CV	Cross-validation
DFS	Disease-free survival
DICOM	Digital imaging and communications in medicine
DT	Decision tree
DWI	Diffusion weighted image
FN	False negative
FOV	Field of view
FP	False positive
GLCM	Gray level co-occurrence matrix
GLDM	Gray level dependence matrix
GLRLM	Gray level run length matrix
GLSZM	Gray level size zone matrix
GNB	Gaussian naïve bayes
HE	Histogram equalization
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion

ICC	Intra and inter-class correlation coefficient
IKN	Institut Kanser Negara
KNN	K-nearest neighbor
LR	Logistic regression
LSIL	Low-grade squamous intraepithelial lesion
ML	Machine learning
MRI	Magnetic Resonance Imaging
MSC	Mean square for columns
MSE	Mean square error
MSR	Mean square for rows
NMR	Nuclear magnetic resonance
NPV	Negative predictive value
PACS	Picture archiving and communication system
PPV	Positive predictive value
RF	Random forests
ROC	Receiver operating characteristic
ROI	Region of interest
ROSE	Recognizing opportunities for service and education
SNR	Signal to noise ratio
Sp	Specificity
SPSS	Statistical package for the social sciences
SVM	Support vector machine
TMN	Tumour node metastasis
TN	True negative
TP	True positive
TPOT	Tree-based pipeline optimization tool
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Research background

Cancer of the cervical represent a worldwide health concern, particularly in low-resource settings. The United States is expected that there will be 1,958,310 new cancer cases and 609,820 cancers related to deaths in 2023 (Siegel et al., 2023). In Malaysia, cancer is the fourth leading cause of death which contributes to 39.3% as stated in the Malaysian study on cancer survival and cervical cancer is the third most common female cancer. According to Shin et al., 2010, the incidence of cervical cancer has shown an upward trend, with an increase in the average age of affected patients. It is estimated that the mortality rate due to cervical cancer among women aged 30 to 60 has significantly increased (Mustafa et al., 2022). Apart from a sedentary lifestyle and unhealthy dietary patterns, more women suffer from cervical cancer. The fast-paced lifestyles inherently neglect routine physical exams, which increases the risk of cervical cancer.

There is variety of medical imaging modality for diagnosis and treatment. Magnetic Resonance Imaging (MRI) that is extensively used for superior tissue structure contrast and tumour evaluation and offer a more detailed understanding of the tumor's microenvironment and microcellular activity (Schick et al., 2019). Detailed knowledge of anatomy and precise tumor localization are essential in radiology for aiding clinicians in diagnosing, prognosticating, and planning treatment decisions. Hence, it is imperative to minimize human error or the possibility of false negatives to the greatest extent possible, as this will impact visual interpretation.

Radiomics gathers quantitative data from medical imaging and uses advanced computer techniques to highlight complex tumor traits. These characteristics, which include shape and geographic interactions, provide insights into tumor biology (Hagiwara et al., 2023). According to the literature, radiomics has the potential to improve cervical cancer prognosis by assessing risk, predicting treatments, and identifying biomarkers (Lambin et al., 2012). It complements traditional assessments by offering a complete approach to disease characterization (Abbasian et al., 2022). Furthermore, insufficient research has been conducted on the radiomics analysis of quantitative cervical cancer in Malaysia, highlighting the necessity to commence this line of investigation. Therefore, this study investigates the present status of cervical cancer radiomics, focusing on the reliability of image segmentation and feature selection.

Through a systematic review of the existing literature, the study identified a deficiency in research on the accuracy, sensitivity, and clinical specificity of radiomics in diagnosing cervical cancer using machine learning techniques. Consequently, this radiomics study is pivotal in advancing the reporting system by providing quantitative data to support medical professionals in interpreting digital images effectively. The current approach to interpreting radiological images of cervical cancer involves only qualitative assessments, which depend on subjective interpretations by radiologists and are recognized to be a time-consuming process (Yunus et al., 2022). This study emphasizes the significance of quantitative analysis for its measurability and enhanced accuracy in clinical evaluation and documentation of cervical cancer classification. Additionally, the application of machine learning methodologies in cervical cancer radiomics research is being explored due to their increasing utilization in the medical field. Growing in the application of artificial technology contributes to advancement in medical imaging field (Hosny et al., 2018).

The growing need in improving cervical cancer detection using machine learning has prompted this study to improve the algorithm implementation that can overcome the limitations in computational and system complexity in cervical cancer detection. The expectation is that the results of this research can be applied in a clinical context to improve patient well-being and promote the role of artificial intelligence of cervical cancer. Diffusion-weighted imaging (DWI) parameters potentially be used as an imaging biomarker to evaluate the effect of b-value at microscopic level (Padhani et al., 2011). DWI is a non-invasive MRI technique that allows for the observation of water molecules' movements within biological tissues and tumour (Shen et al., 2015). This research offers into radiomics and machine learning algorithm in classification in cervical cancer clinical imaging protocols which essential for evaluating the effectiveness of cancer treatments and patient survival.

1.2 Problem statement

Current practice in radiological image interpretation of cervical cancer relies solely on qualitative assessments, involving subjective interpretation of images by radiologist, which are known to be time-consuming (Yunus et al., 2022). Images information in pixel contain important role in human perception, which limited to visualize the information of electromagnetic (EM) spectrum. Moreover, both random sampling biopsy and surgical procedures for diagnosis have limitations, such as procedure-related complications, sampling errors, and interobserver variability. Consequently, interobserver variability and false-negative diagnoses are inevitable, as human error can impact both diagnosis and prognosis for the patient (Balaji & Chidambaram, 2022). Furthermore, early screening with combination of radiomic machine advancement created new opportunities to study medical signal processing, enabling analysis to become more intelligent and effective.

The radiomics process is also capable of significantly assisting the field of medical imaging in two distinct steps namely, the process of data segmentation and classification. Analyzing data that requires human interaction on selection of a specific region of interest (ROI) to complete quantitative analysis in the clinical routine. However, there are variety of segmentation techniques that can be used in phase of tumor segmentation. The component of radiomic represents high quantitative image features of tumor phenotypes that characterize the volumes of interest. The feature extraction contains information from input images and represents data in lower dimensional space (Scrivener et al., 2016). This involves a complex mathematical algorithm which describes phenotypes of tumors that are unrecognized and might not be detectable by human observation.

The influence on the repeatability features is also known to be affected by the large variability of image acquisition and feature extraction parameters (Zhang et al., 2017). Moreover, there are several segmentation techniques that can be utilized in the process of image segmentation (Seo et al., 2020). Identifying the segmentation technique that offers greater stability in radiomic features of cervical cancer is crucial. Hence, it is essential to identify the segmentation technique that provides more stability in the radiomic features of cervical cancer. This determination can enhance the precision of tumor edge delineation, boundaries, and contrast, ultimately improving the consistency in extracting radiomic features.

Moreover, the integration of machine learning methodologies in cervical cancer radiomics research is highly regarded for its applicability in the medical field. This research in radiomics has the potential to decrease the workload for specialist physicians by enhancing the accuracy of diagnostic reports. It can reduce the need for manual input by specialists in describing the intensity, shape, and texture of anomalies in images and the boundaries of cancer, thereby improving patient care and treatment.

1.3 Research objectives

The main objective of this research study is to design a model for classifying cervical cancer DWI-MRI images using radiomic features and machine learning techniques. The specific objectives are:

1. To evaluate the stability of reproducibility and repeatability of radiomic features DWI-MRI images of cervical cancer.
2. To determine the impact of the contrast enhancement in the stability of radiomic features cervical cancer DWI-MRI images.
3. To analyze the performance of supervised machine learning classifier in differential radiomic of cervical cancer DWI-MRI images.
4. To compare the performance of support vector machine (SVM) in classifying the DWI-MRI b-value for cervical cancer images.

1.4 Scope of study

The scope of this study involves determination of the radiomics features from various segmentation techniques and contrast enhancement of cervical cancer DWI-MRI images. Afterward, evaluating the performance of classifier using radiomic features and machine learning classifier. The scope of the study was divided into four parts:

1. Part I: The contrasted MRI pelvis of cervical cancer with DWI-MRI images were segmented using manual and semi-auto segmentation technique using active contour model (ACM) algorithm to evaluate the stability of reproducibility and repeatability of radiomic features.

2. Part II: The contrast enhancement using contrast limited adaptive histogram equalization (CLAHE) in the stability of radiomic features cervical cancer DWI-MRI images were compared between manual, semi auto segmentation and segmentation with CLAHE.

3. Part III: The performance of supervised machine learning classifiers in differentiating radiomic features of cervical cancer DWI-MRI images was evaluated using selected features. The classifiers applied included logistic regression (LR), decision trees (DT), and support vector machines (SVM).

4. Part IV: The performance of SVM were analyzed in classifying the DWI-MRI b-value for cervical cancer staging.

1.5 Research significance

Early-stage in patients of cervical cancer in low-risk and high-risk groups show different radiomic scores of DWI-MRI in estimating disease-free survival (DFS) (Hu et al., 2022). The different radiomic scores provide a better understanding of high-risk and low-risk groups, patient treatment planning, response to anticancer therapies, drug development, and making patient decisions. DWI-MRI plays a crucial role in radiomics for various cancer types. It quantitatively measures apparent diffusion coefficient (ADC), which reflects water diffusivity, and provides information on cell membrane integrity and tumor cellularity. Images acquired from DWI-MRI were utilized because of their ability to serve as an initial surrogate imaging biomarker for therapy responsiveness. Moreover, DWI-MRI has been identified as valuable in the evaluation of cervical cancer, providing essential information for diagnosis and treatment planning. Zhang et al., (2022a) demonstrated that radiomics models with a combination of multi-parametric DWI showed high clinical value in predicting concurrent chemoradiotherapy for cervical cancer.

Manual segmentation, though widely used, is often labor-intensive, time-consuming, and subject to variability due to human error (Gresser et al., 2023). Segmentation using DWI-MRI images improves tumor delineation with the utilization of ACM algorithm in semi auto segmentation which produce more stability in reproducibility and repeatability of features extraction. Impact of contrast enhancement using CLAHE in the stability of radiomic features cervical cancer DWI-MRI images were produce higher level of robustness compare to manual and semi-auto segmentation method. Thus, CLAHE segmentation improved the consistency and durability of radiomic features segmentation and strengthening the robustness of radiomic features for staging classification. Performance evaluation using a supervised machine learning classifier in the differential radiomics of cervical cancer DWI-MRI images is important for further development of model selection in machine learning classification models. Previous research in cervical cancer detection and staging has utilized various machine learning models, including DT, random forests (RF), k-nearest neighbors (k-NN), and artificial neural networks (ANN)(Yu et al., 2024).

These models have demonstrated varying degrees of success, with RF and ANN showing particularly strong performance in image classification tasks. However, SVM has remained popular due to its robustness with smaller datasets and its ability to handle complex decision boundaries effectively. Lastly, the performance of SVM in classifying the DWI-MRI b-value for cervical cancer staging improves the understanding of effective b-values in radiomic features. The research makes a significant contribution by reducing scanning time in the clinical application of DWI-MRI sequences.

The research findings result a valuable tool to assist specialist physicians in achieving more precise disease diagnoses. Many studies have recently published that machine learning has many advantages over complexity and accuracy issues in conventional methods (Bayrak & Kirci, 2022; Zhou et al., 2022). Applying machine learning based classification in combination with preconditioning, redundancy, and dimensional reduction can enable the extraction of quantitative imaging features to diagnose cervical cancer (Reijtenbagh et al., 2022). Thus, this research comprehensively studies radiomic features of cervical cancer through DWI-MRI images and performance of machine learning model to enhance the accuracy of the classifier.

The multi-center radiomics study in Malaysia was initiated in response to significant challenges posed by the existing limitations of MRI technology, particularly in the quantitative identification of cervical cancer. By employing radiomic machine learning algorithms across multiple healthcare institutions in Malaysia, this study aims to enhance the diagnostic capabilities for individualized patient care. In other words, this research implementation indirectly encourages non-professional physicians to perform early diagnosis and individual screening if any symptoms occur. Hence, the timely identification of cervical cancer through machine learning and the application of radiomic assessments enable the assessment of cancer stage using DWI images more effectively. This is in compliance with the United Nations Sustainable Development Goals 3 (SDG 3), which aims at encouraging healthy lives to every person and promote well-being for individual at all ages including cancer screening. The anticipated outcomes include improved efficiency and accuracy in disease diagnosis, with potential benefits for the Ministry of Health Malaysia, private healthcare providers in the country, as well as patients both domestically and internationally. In conjunction with SDG 9, to develop innovative machine learning software for cervical cancer, and SDG 11, to strengthen global partnerships in the study of cancer.

1.6 Thesis outlines

This thesis consists of five-chapter, chapter 1 introduced along with the critical issues in the field. The chapter briefly discusses the research background, defines the problem, states the purpose and underscores the significance in this study. Chapter 2 provides the background of the study, which explains the introduction of the reproductive system, cervical cancer disease, the history and principle of MRI are elaborated. Within this chapter, the discussion extends to the radiomic features correlated with cervical cancer, along with the comprehensive procedure for cervical cancer detection, which includes preprocessing, segmentation, feature extraction, and classification. Chapter 3 explains the research methodology by conceptual design, followed by the dataset employment and algorithm development. Chapter 4 discusses result and analysis from the methodology of the proposed work. Lastly, Chapter 5 presents the research conclusion, followed by the findings, limitations arising from the analysis performance and necessary future recommendations.

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