UNIVERSITI PUTRA MALAYSIA

RADIATION DOSE, CANCER RISK AND DIAGNOSTIC PERFORMANCE OF COMPUTED TOMOGRAPHY PULMONARY ANGIOGRAPHY EXAMINATION

HANIF BIN HASPI HARUN

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By

HANIF BIN HASPI HARUN

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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Concerns towards high radiation dose and cancer risk from Computed Tomography Pulmonary Angiography (CTPA) examinations have prompted efforts to develop a novel optimization while preserving CT image diagnostic performance. Hence, this study aims to evaluate the radiation dose, cancer risk and image diagnostic performance of CTPA examination regarding primary and secondary optimization such as iterative reconstruction (IR) algorithm, tube potential and pitch factor selection. The first phase of this thesis begins with the establishment of a local Diagnostic Reference Levels (DRL) with respect to image quality together with evaluation of organ dose and cancer risk. 127 subjects (55 men and 72 women) with an age range from 18 to 88 years old who were suspected of having PE and underwent CTPA examination were recruited. Dose descriptors such as volume-weighted CT Dose Index ($CTDI_{vol}$), Size-Specific Dose Estimates (SSDE), Dose Length Product (DLP) and effective dose (E) were recorded and analyzed together with noise as the image quality. Body sizes of the subjects were categorized based on their effective diameter (ED) length and divided into three groups: P1 (19–24 cm), P2 (24–29 cm), and P3 (29–34) cm. There is a significant difference in local DRL values and between body sizes ($p < 0.05$) while noise is not significantly different between body sizes ($p > 0.05$). Organ dose and cancer risk were estimated by the CT-EXPO (Ver 2.5.1, Germany) and recommendation from the International Commission on Radiological Protection Publication (ICRP) 103 report respectively according to the primary beam. In one million CTPA examinations, the risk of cancer in breast, lung and liver organs was 0.009%, 0.007%, and 0.005%, respectively.

The second phase focuses on the diagnostic performance assessment. Different levels of IR algorithms were applied in routine CTPA and several modified tube potentials. The value of signal and noise were defined by placing the circular region of interest (ROI) on the main pulmonary artery (MPA), right pulmonary artery (RPA), left pulmonary artery (LPA), ascending aorta (AA), and descending aorta (DA). The performance of each protocol was presented as Signal to Noise Ratio (SNR), Contrast to Noise Ratio (CNR) and Figure of Merit (FOM). CNR and FOM performed significantly better when IR algorithm levels were increased, tube potential was reduced, and if patients had smaller body sizes ($p < 0.05$) while fluctuation trends were observed in SNR. The last phase of this thesis covers the assessment of diagnostic performance by a CATPHAN 600 phantom with primary and secondary optimization. The phantom was scanned with CTPA local protocol using different tube potentials and pitch factors. Images obtained were reconstructed with the IR algorithm (levels 3, 4 and 5). Diagnostic performance was quantified objectively by imQuest software (version 7.1, Duke University, USA). Noise power spectrum (NPS), target transfer function (TTF), CNR and SNR were evaluated concerning the optimization setting. It was found that the CNR value was increased while NPS was degraded by increasing IR levels. Noise value reduction has significantly achieved the increase of tube potential although there are no changes in TTF values. The alteration of pitch factor provides some fluctuation pattern of both NPS and TTF values. Future research could be carried out with different types of examinations, scanner models and substantive phantoms to expand these assessment methods proposed in this study. It is also recommended to extend a subjective diagnostic performance measurement to increase the reliability of the objective measurement attained. The study discovered a novel finding of the characterization of radiation dose, cancer risk and diagnostic performance with a different type of quantitative measurement for local CTPA examination.

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

DOS RADIASI, RISIKO KANSER DAN PRESTASI DIAGNOSTIK BAGI PEMERIKSAAN TOMOGRAFI BERKOMPUTER ANGIOGRAFI BAHAGIAN PULMONARI

Oleh

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Kebimbangan terhadap dos sinaran yang tinggi dan risiko kanser dari pemeriksaan Tomografi Berkomputer Angiografi Pulmonari (CTPA) telah mendorong usaha untuk membangunkan pengoptimuman baru bagi mengekalkan prestasi diagnostik imej CT. Oleh itu, kajian ini bertujuan untuk menilai dos sinaran, risiko kanser dan prestasi imej diagnostik bagi pemeriksaan CTPA mengenai faktor primer dan sekunder seperti algoritma pembinaan semula lelaran (IR), potensi tiub dan pemilihan faktor nada. Fasa pertama tesis ini bermula dengan membangunkan tahap rujukan diagnostik (DRL) tempatan berkenaan dengan kualiti imej serta penilaian dos organ dan risiko kanser. 127 subjek (55 lelaki dan 72 perempuan) dalam julat umur 18 hingga 88 tahun yang disyaki mempunyai PE dan menjalani pemeriksaan CTPA direkrut. Deskriptor dos seperti indeks dos CT berwajaran volum ($CTDI_{vol}$), anggaran dos berdasarkan saiz khusus (SSDE), hasil darab panjang dos (DLP), dos efektif (E) direkod dan dianalisa serta hingar sebagai kualiti imej. Saiz badan subjek dikategori berdasarkan kepada panjang diameter efektif (ED) dan dibahagikan kepada tiga kumpulan: P1 (19–24 cm), P2 (24–29 cm), and P3 (29–34) cm. Terdapat perbezaan yang signifikan dalam DRL tempatan dan antara saiz badan ($p < 0.05$) manakala hingar tidak mempunyai perbezaan yang signifikan antara saiz badan ($p > 0.05$). Dos organ dan risiko kanser dianggarkan masing-masing melalui perisian CT-EXPO (Ver 2.5.1, Germany) dan perakuan daripada Laporan Suruhanjaya Antarabangsa bagi Penerbitan Perlindungan Radiologi (ICRP) ke-103 berdasarkan kepada alur primer. Dalam satu juta pemeriksaan CTPA, risiko kanser bagi organ payudara, paru-paru dan hati masing-masing sebanyak 0.009%, 0.007%, and 0.005%.

Fasa kedua memfokuskan pada penilaian prestasi diagnostik. Tahap algoritma IR yang berbeza digunakan dalam CTPA rutin dan beberapa modifikasi protokol. Nilai isyarat dan hingar ditentukan dengan meletakan rantau yang dikehendaki (ROI) berbentuk bulat pada pulmonari arteri utama (MPA), pulmonari arteri kanan (RPA), pulmonari arteri kiri (LPA), aorta menaik (AA) dan aorta menurun (DA). Prestasi setiap protokol ditunjukkan sebagai nisbah isyarat kepada hingar (SNR), nisbah kontras kepada hingar (CNR) dan angka berguna (FOM). CNR dan FOM menunjukkan prestasi yang lebih baik apabila tahap algoritma IR meningkat, potensi tiub menurun dan jika pesakit mempunyai saiz badan yang lebih kecil ($p < 0.05$) manakala trend berubah-ubah diperhatikan pada SNR. Fasa terakhir tesis ini merangkumi penilaian prestasi diagnostik oleh fantom (CATPHAN 600) dengan pengoptimuman primer dan sekunder. Fantom ini diimbas dengan protokol CTPA tempatan menggunakan potensi tiub dan faktor nada yang berbeza. Gambar terhasil dibina semula dengan tiga tahap algoritma IR yang berbeza (tahap 3,4 dan 5). Prestasi diagnostik ditentukan secara objektif menggunakan perisian imQuest, (versi 7.1, Universiti Duke, Amerika Syarikat). Spektrum kuasa hingar (NPS) dan fungsi pemindahan sasaran (TTF), CNR dan SNR dinilai telah dinilai berkenaan tetapan pengoptimuman. Didapati bahawa nilai CNR meningkat manakala NPS terjejas dengan meningkatnya tahap IR. Penurunan nilai hingar dicapai secara signifikan bagi peningkatan potensi tiub walaubagaimanapun tiada perubahan pada nilai TTF. Perubahan pada faktor nada menghasilkan trend berubah-ubah bagi nilai NPS dan TTF. Kajian masa depan boleh dijalankan pelbagai jenis pemeriksaan, model pengimbas dan fantom yang substantif untuk mengembangkan kaedah penilaian yang dicadangkan dalam kajian ini. Ia juga disyorkan untuk melanjutkan pengukuran prestasi diagnostik subjektif untuk meningkatkan kebolehpercayaan pengukuran objektif yang dicapai. Kajian ini menghasilkan penemuan baru mengenai ciri-ciri dos sinaran, risiko kanser dan prestasi diagnostik dengan jenis pengukuran kuantitatif yang berbeza untuk pemeriksaan CTPA tempatan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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AA	Ascending Aorta
AAPM	American Association of Physicist in Medicine
AD	Achievable Dose
ALARA	As Low as Reasonably Achievable
ART	Algebraic Reconstruction Technique
AP	Antero-Posterior
ASIR	Adaptive Statistical Iterative Reconstruction
ATCM	Automatic Tube Current Modulation
BEIR	Biological Effects of Ionizing Radiation
BMI	Body Mass Index
CNR	Contrast to Noise Ratio
CT	Computed Tomography
$CTDI_{vol}$	Volume weighted Computed Tomography Dose Index
CTPA	Computed Tomography Pulmonary Angiography Examination
DA	Descending Aorta
DECT	Dual Energy CT-Scan
DFT	Discrete Fourier Transform
DNA	Deoxyribonucleic acid alteration
DLP	Dose Length Product
DRL	Diagnostic Reference Level
DVT	Deep Venous Thrombosis
E	Effective Dose
ED	Effective Diameter
EMI	Electrical and Music Industries
ESF	Edge Spread Function
FBP	Filter-Back Projection
FOM	Figure of merit
FOV	Field of View
HIR	Hybrid Iterative Reconstruction
HU	Hounsfield Units
ICRP	International Commission on Radiological Protection
IR	Iterative Reconstruction
IIR	Image-based Iterative Reconstruction
ICRP	International Commission on Radiological Protection
KeV	kiloelectron volt
kVp	Kilovoltage peak
LAT	Lateral
LCD	Low Contrast Detectability
LPA	Left Pulmonary Artery

LSF	Line Spread Function
mAs	Milliampere-seconds
MBIR	Model-based Iterative Reconstruction
MDCTA	Multi-Detector Computed Tomography Angiography
MEI	Monochromatic Energy Images
MOH	Ministry of Health Malaysia
MPA	Main Pulmonary Artery
MREC	Medical Research and Ethics Committee
MSAD	Multiple Scan Average Dose
MSCT	Multi-slice Computed Tomography
MTF	Modulation Transfer Function
NCRP	National Council on Radiation Protection and Measurements
NPS	Noise Power Spectrum
NPV	Negative Predictive Value
PE	Pulmonary Embolism
QA	Quality Assurance
R	Cancer Risk
RPA	Right Pulmonary Artery
SAFFIRE	Sinogram-Affirmed Iterative Reconstruction
SD	Standard Deviation
SNR	Signal to Noise Ratio
SSDE	Size-Specific Dose Estimates
TLD	Thermo-Luminescent Dosimeters
TTF	Target Transfer Function
TTP	Time to Peak
VNC	Virtual Non-Contrast Image
VMI	Virtual Monoenergetic Images
VTE	Venous Thromboembolic

CHAPTER 1

INTRODUCTION

1.1 Research Background

The discovery of X-rays in 1895 ushered in a new era in medicine that aids the visualization of the human body without the need for painful or life-threatening operations. Because of its capability, the discovery was acknowledged almost immediately and accepted as a modern treatment diagnostic technique. Computed tomography (CT) examination is a promising imaging tool that uses a device to generate three-dimensional (3D) images that are important for screening, diagnosis, therapy, and patient care management. Figure 1.1 illustrated the first CT Scanner introduced by Godfrey Hounsfield in 1973, which consisted of a rudimentary scanner gantry and control console. It has now become one of the most popular tools in diagnostic imaging, with 221 million CT exams conducted worldwide each year, with the number continuously growing (UNSCEAR, 2010).

Figure 1.1: Illustration of old CT-scanner gantry (left) and control console (right) (Hounsfield, 1973)

CT Pulmonary Angiography (CTPA) is one of the CT imaging techniques that enable the visualization of pulmonary arteries to enable diagnosis and treatment of Pulmonary Embolism (PE) as illustrated in Figure 1.2. PE is a condition when a clot blockage inside the pulmonary arteries interrupts the circulation of the blood in a respiratory system (Heit *et al.*, 2000). PE is considered a significant health condition associated with high mortality and requires rapid and accurate diagnosis, particularly in patients at high risk. Through the advancement of CT technology, more than 90% of acceptable PE detection can be achieved and demands of the CTPA examination are steadily growing.

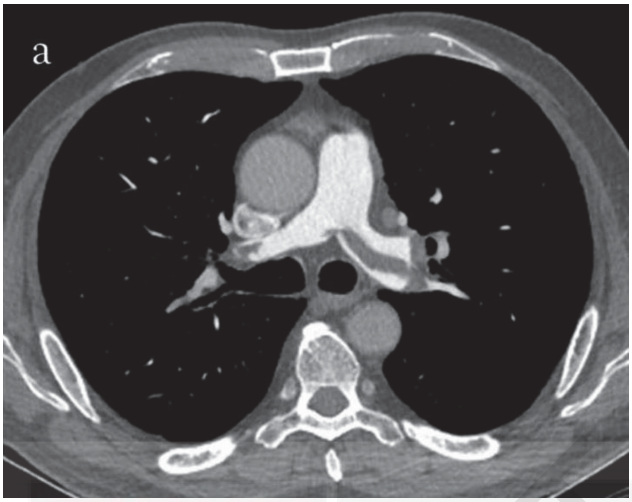

Figure 1.2: A CT-images of 64-year-old man with pulmonary embolism (Hu *et al*., 2017)

In 2001, the International Commission on Radiological Protection (ICRP) raised an alarm, stating that the use of CT was growing and that the dose exposure from CT examinations was higher than from other imaging modalities (Foley *et al*., 2012). In concerned with ionizing radiation, the ICRP was the first to discuss radiation safety principles. In 1990, and later mentioned in 1996, the International Commission on Radiological Protection (ICRP) issued a document that defined two crucial components for the principal in medicine, which is justification and radiology examination optimizations. Justification implies that the necessity of ionizing radiation is a benefit of the patient exceeds any potential harm. Optimization means that radiation exposure is optimized for clinical purposes of the exam which is the ionizing radiation needed is essential for clinical purposes (Kanal *et al*. 2017).

According to National Council on Radiation Protection and Measurements (NCRP), radiological examination by using CT-Scan caused to significantly higher collective effective dose (E) is estimated to account for up to 63% of the total as shown in Figure 1.3 (NCRP, 2019). Hence, it is useful to examine the cause of the higher dose contribution of CT scan examination and currently several studies investigating the different types of X-ray modalities that contribute to the different radiation dose levels (Rehani *et al*. 2012). The requirement of optimization in specific scan protocols is needed to implement an appropriate As Low As Reasonably Achievable (ALARA) principle. The dose exposure level was customize based on patient age or size, region of imaging and clinical indication to assure the dose exposure to the patient are put as reasonably low without compromising diagnostic quality for all clinical purpose of radiological examination especially CT examination.

There are obvious tradeoffs between dose exposure and image quality with parameter adjustability to reduce dose exposure. It is very subjective when explained about the diagnostically accepted in radiological examination that is dependent on the clinical task involved. For example, by reducing the tube current in CT-Scan examination, the radiation dose is also reduced but increases the noise of the image by 1.41 or 41% by reducing half of it. This will lead to inadequate low contrast resolution performance. By increasing the speed of the table or pitch factor, can also reduce the dose exposure but can degrade the z-axis resolution and the scan length become over-ranging from the planned image boundaries. Meanwhile, reducing tube potential in the examination to reduce dose exposure may contribute to the beam hardening artifact in the CT images especially in the lowest tube potential available in CT scanner (exp: 80 kilovoltage peak (kVp)) (McNitt-Gray, 2006).

Figure 1.3: The collective effective dose found to increase significantly from 2006 to 2016 for CT examination (NCRP, 2019)

CT image quality is essential for high-quality diagnostics to provide beneficial reporting of patient conditions. The CT scan emits a constant X-ray continuum along the x-y axis in rotating mode along the z-axis during scan acquisition and provides a homogeneous distribution of X-ray radiation in human tissues. Technical developments offering novel imaging facilities, a reduction of exposure and improved image qualities have resulted in greatly increased use of CT systems as seen in Figure 1.4. The optimization of a CT examination is achieved when image quality enables the clinical question to be answered while keeping low dose exposure towards the patient (Hart *et al*. 2008). This goal is, however, difficult to apply in practice due to a wide range of parameters dependent such as acquisition time, temporal resolution, and energy resolution when dealing with kV optimization or spectral CT imaging, and other factors. While image quality has always been a concern for the physical community, the quality of the clinically acceptable image has become more of an issue as a strategy to reduce radiation dose to a greater focus.

Diagnostic image quality cannot be fully assessed without the knowledge of the anatomical area of interest and pathology to be searched for. Due to that, many different anatomical phantoms have been developed, such as cardiac, liver, lung, thorax phantoms, among others (Karim *et al*. 2016a). These are having different in texture, density, size, and complexity. The reconstruction kernel is a feature that is capable to cater the variation of human body tissue. It is defined as the image processing filter applied to the raw data to yield a final scan image (Sauter *et al*. 2018). The sharpness of the final image is more strongly influenced by the type of filter used, often known as the soft and sharp kernel. A soft convolution kernel can smooth edges and minimize image noise, which is useful in obese patients where the signal-to-noise ratio (SNR) can be reduced due to adipose tissue attenuation. Sharp convolution kernels improve edges at the expense of increased overall image noise, which can obscure certain visual information (Ministry of Health, 2013). The kernel setting selection may be different based on specific clinical indications and diagnostic requirements. For instance, a soft kernel is typically used in brain checks or liver tumors assessment to reduce noise and increase low contrast detectability (LCD), while sharp kernels are commonly used in exams to obtain higher spatial resolution such as lung examination and assess the structure of concrete bones.

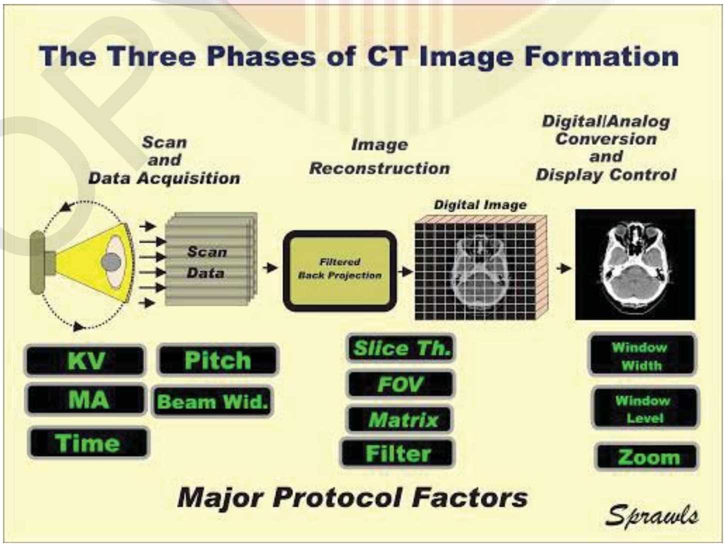

Figure 1.4: Three phases of CT image formation with compensation between dose exposure and image quality ("Safety of CT Scan," 2016)

The noise in CT images may increase in some conditions or examinations using thinner slice thickness or high spatial frequency filters with all variables kept constant. To achieve better images, it should eliminate noise by increasing tube current, resulting in higher radiation exposure to the patient (Goo, 2012). Different clinical tasks have different requirements for image quality such as high, medium and low signal-to-noise task is required for solid nodule detection in the lung, ruling out bleeds in the brain and kidney lesion detection, respectively (McNitt-Gray, 2006). When moving from axial scanning to helical scanning to multi-detector helical scanning, the consideration of slice thickness selection of the reconstructed image becomes much more intricate and complicated. This thesis is focusing on the width of the reconstructed slice in the helical scanning and the factors that may affect it, which may include collimation beam X-ray (especially in a single CT slice scanner), the width of the detector (especially in multi CT-detector scanner), helical / table helical speed and helical interpolation algorithm. For some manufacturers' multi-detector scanners, the reconstructed slice thickness is independent of table speed; this is because of the interpolation algorithm used (McNitt-Gray, 2006).

1.2 Problem Statement

CTPA promotes excellent diagnostic accuracy in the diagnosis of PE, but it includes a high dose exposure of up to 2 mSv of E, which raises the risk of radiation-induced cancer in populations (Halid *et al*., 2018; Leithner *et al*., 2018). Since the use of CT is increasing and there is a lack of justification among practitioners, it is essential to optimize CTPA examinations by establishing Diagnostic References Level (DRL) (Vañó *et al*., 2017). The DRL is widely established by various countries and institutions as a baseline of the radiation dose administered to the patient, but it does not take into account factors that affect the DRL value, such as scanner type, patient size, and clinical indication. It is essential to develop a meaningful DRL concerning the above factors to ensure a positive CT examination optimization strategy. As highlighted by the ICRP, the association of DRL of patients with image quality is significant (Vañó *et al*., 2017). For image quality descriptors, it will be necessary to identify benchmarks such as spatial resolution, noise spectra, and contrast with other dose metrics, such as Dose-Length Product (DLP), Size-Specific Dose Estimates (SSDE), organ dose and E (Ria *et al*., 2019; Vañó *et al*., 2017). Previous research provides an assessment of estimating cancer risk for various types of CT examination however it is only tailored to a general population exposure rather than to an individual patient (Lahham *et al*., 2018; Halid *et al*., 2018; Karim *et al*., 2017; (Saltybaeva *et al*., 2016). Instead, the organ dose and cancer risk are appropriately assessed while subjects or body characteristics are taken into account. Both assessments varied in different conditions, dependency on age, sex and population studied (Muhammad *et al*., 2019; Karim *et al*., 2017; Sarma *et al*., 2012).

Sauter *et al*., (2018) and Dane *et al*., (2018) suggest that optimization in CT examination such as alteration of tube potential, IR algorithm and patient habitus are needed by compensation between radiation dose and image quality. It has been reported that diagnostically accepted image quality of CTPA can be achieved by decreasing the tube potential of 100 kVp or even as low as 80 kVp, and dose reduction strategy also accomplished (Dane *et al*., 2018; Sauter *et al*., 2018). However, an inappropriate selection of tube potential can cause noisy images, especially for an obese patient. Thus, the degradation of image quality led to a false-negative diagnosis of PE in CTPA examination. Previous studies have found a strong relationship between dose exposure and image quality concerning the Body Mass Index (BMI) as a patient size metric (Kim *et al*., 2018; Megyeri *et al*., 2015; Szucs-Farkas *et al*., 2014). However, the impact of an effective diameter as a patient size metric and tube potential concerning both the above parameters has not been evaluated so far in CTPA.

A heterogeneous tissue element on real patients limits the task-based assessment of image quality that only selected metrics can be defined (Lahham *et al*., 2018). For instance, spatial domain measurement in real patients depends solely on the manipulation of a pixel, such as signal to noise ratio (SNR), a contrast to noise ratio (CNR), which has become inadequate indicators of diagnostic performance. Instead, a phantom serving as a substitute for real patients is constructed using various modules that enable to cater an accurate quality metrics such as frequency domain analysis which is greatly dependent on noise fluctuation and edge enhancement in distinct spatial frequencies (Greffier *et al*., 2020). Several studies focus on the task-based assessment of CT by different scanner types and dose exposure without considering specific CT examination protocols. Their findings may not portray the absolute characterization of the image quality which is not suited to apply with a specific protocol, scanning type and clinical indications. Figure 1.5 shows schematically the research framework and issues to resolve from the study. It is intended to provide information on the issues of current dosimetry and diagnostic quality in CT examination. In the future, this thesis could also be used as the first step of baseline information on the recent situation of CT optimization in Malaysia.

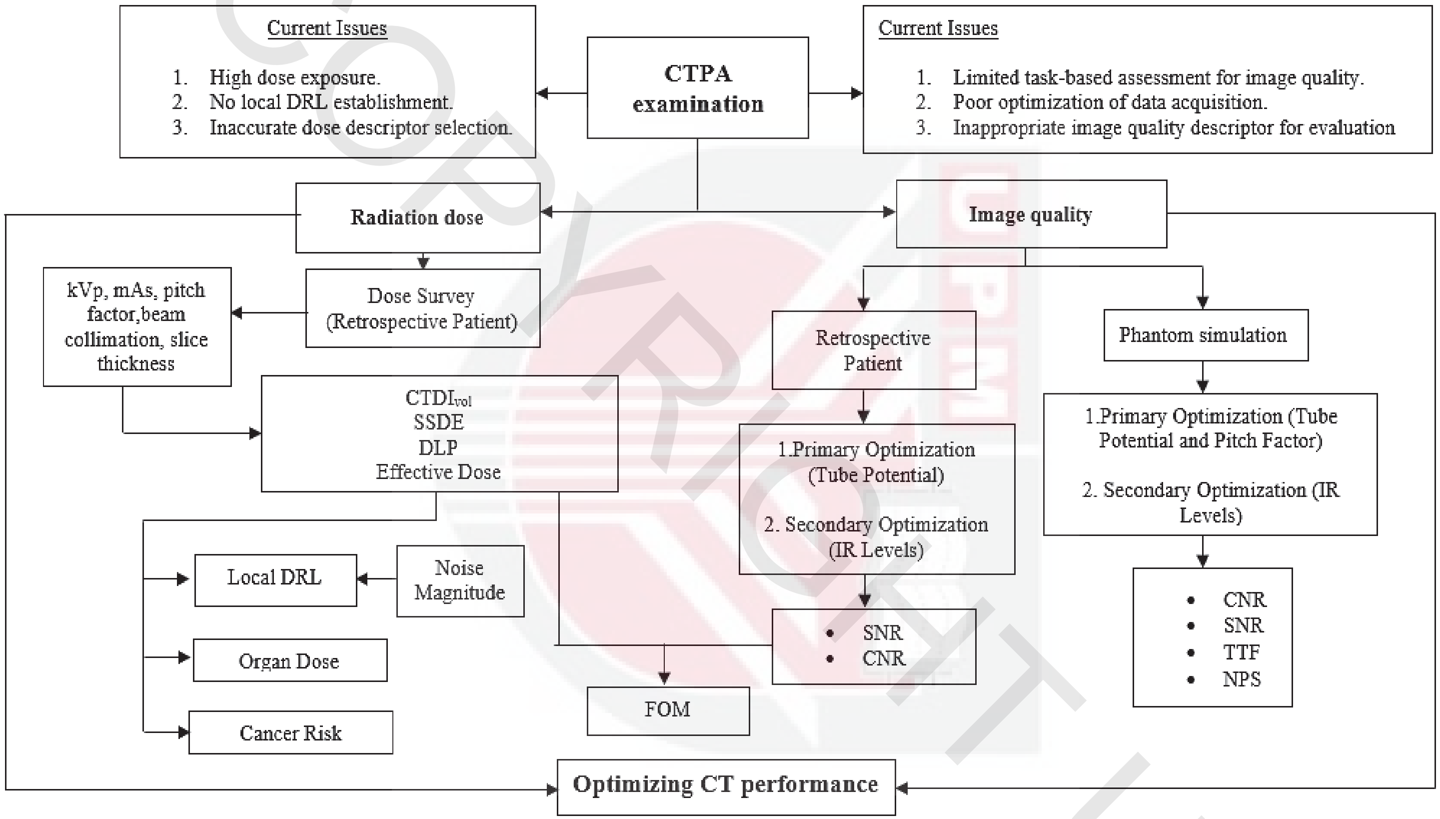

Figure 1.5: Research framework of this study

1.3 Research Question

The aim of the study was to answer certain research questions which are:

1. What is the value of local DRL and image quality references level compare to other countries in CTPA?

2. What is the radiation-induced risk from CTPA examination in subjects characteristic?

3. What is the effects of the the IR algorithm, tube potential and patient habitus on diagnostic performance in retrospective patients?

4. What is the relationship of selected primary and secondary optimization with the diagnostic performance by a simulated phantom?

1.4 Research Objective

1.4.1 General Objective

The present study aims to evaluate the radiation dose, cancer risk and image quality performance of CT Pulmonary Angiography Examination in regards to primary and secondary factors such as IR reconstruction, tube potential and pitch factor selection.

1.4.2 Specific Objective

1. To determine and establish local DRL with regard to image quality references level and compared with CTPA practices in other countries.

2. To evaluate the radiation-induced risk from CTPA examination based on the subjects characteristic.

3. To assess the effects of the IR algorithm, tube potential and patient habitus on diagnostic performance in retrospective patients by establishing the FOM index.

4. To determine the relationship of selected primary and secondary optimization with the diagnostic performance by a simulated phantom.

1.5 Significant Contribution of Study

DRLs are frequently used in various countries and clinical institutions for diagnostic purposes. With image quality reference levels becoming essential as a guideline for clinicians to perform CT examinations with a balance of diagnostic performance and dose exposure. Previous research has successfully evaluated the cancer risk in a variety of CT examinations and scanner types, despite solely relying on the dose exposure and not the patient's characteristics. In terms of cancer risk assessment, this study wants to emphasize the importance of calculating the risk based on the patient's age and gender to accurately estimate the cancer risk. Image quality assessment was not widely implemented in clinical institutions, particularly in Malaysia. This study attempts to establish a baseline or technique of image quality assessment that can be used in clinical practice to attain CT optimization.

1.6 Thesis Outline

This thesis is divided into five chapters. The first chapter discusses the research background, problem statement, research objective, and thesis outline. It provides a summary of the research topic and the importance of the study. Chapter 2 includes information from prior work on literature relevant to X-ray fundamentals, CTPA procedure, radiation dose and image quality descriptor, and optimization strategy for both radiation dose and image quality. The remaining subtopics include detailed explanations of the theory, concept, and formula used in the present study.

Chapter 3 presents the instruments and tools employed in this research and experimental flows includes of the radiation dose, cancer risk and image quality evaluation following the research objective. Chapter 4, focused on a result obtained for local DRL evaluation, radiation dose and cancer risk of the CTPA examination. The image quality evaluation by the retrospective image of patients and phantom was explored based on the effect of IR levels, tube potential, pitch factor and patient sizes. In addition, the detailed discussion regarding the new finding of this study was compared with the previous works. The last chapter (Chapter 5) concludes the main results produced in this research and some suggestions for future research.

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