DOSIMETRIC STUDY OF FLETCHER'S APPLICATOR IN HIGH-DOSE-RATE (HDR) BRACHYTHERAPY FOR CERVICAL CANCER: TLD MEASUREMENTS IN PELVIC WATER PHANTOM

By

MUHAMMAD NURSYABIL BIN SALLEHUDIN

SCHOOL OF HEALTH SCIENCES

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MUHAMMAD NURSYABIL BIN SALLEHUDIN

Dissertation submitted in partial fulfilment of requirement for the degree of Bachelor of Health Science (Honours) (Medical Radiation)

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CERTIFICATE

This is to certify that the dissertation entitled 'Dosimetry Analysis of Fletcher's Applicator in High Dose Rate (HDR) Brachytherapy for Cervical Cancer: TLD Measurement in Pelvic Water Phantom" is the bona-fide record of research work done by Muhammad Nursyabil Bin Sallehudin (150113) during the period of October 2023 to June 2024 under my supervision. I have read this dissertation and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation to be submitted in partial fulfilment for the degree of Bachelor of Health Sciences (Hons) (Medical Radiation). Research work and collection of data belong to the Universiti Sains Malaysia.

Signature of Supervisor

AP Dr. Mohd Zahri Abdul Aziz
Department of Biomedical Imaging
Advanced Medical & Dental Institute
Universiti Sains Malaysia
Bertam. 13200 Kepala Batas,
Pulau Pinang, Malaysia

Date

Signature of Co-Supervisor

Mr. Reduan Abdullah
Medial Radiation Programme
School of Health Sciences
Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia

Date

DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at Universiti Sains Malaysia or other institutions, I acknowledge that the research work and collection of data belong to Universiti Sains Malaysia. I grant Universiti Sains Malaysia the right to use the dissertation for educational or further research purposes.

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LIST OF SYMBOLS

%	Percentage
±	Plus or minus
≤	Less or equal than
≥	More or equal than
°	Degree
C	Coulomb
cm^3	Centimetre cube
$D_{X\%}$	Dose received by X percent volume of structure
D_{Xcc}	Dose received by Xcm^3 volume of structure
Gy	Gray
$V_{X\%}$	Volume of structure that received X percent of prescribed dose
μ	Micro-
π	pi value

LIST OF ABBREVIATIONS

AAPM	American Association of Physicist in Medicine
ABS	American Brachytherapy Society
AMDI	Advanced Medical and Dental Institute
ANOVA	Analysis 0f Variance
CI	Conformity Index
Cov	Coefficient of Variation
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DVH	Dose Volume Histogram
EBRT	External Beam Radiation Therapy
EQD2	Equivalent Total Dose in 2Gy Fraction
ESTRO	European Society for Radiotherapy and Oncology
FIGO	Federation Internationale De Gynécologie Et d'Obstetrique
GEC-ESTRO	Groupe Européen De Curiethérapie-European Society for Radiotherapy and Oncology
GTV	Gross Tumour Volume
HDR	High-Dose Rate
HI	Homogeneity Index
HIPO	Hybrid Inverse Planning and Optimisation

HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HU	Hounsfield Unit
IAEA	International Atomic Energy Agency
IBM	International Business Machines Corporation
IC	Ionization Chamber
ICRU	International Commission on Radiation Unit and Measurement
IMRT	Intensity Modulated Radiation Therapy
IPSA	Inverse Planning Stimulated Annealing
LDR	Low Dose Rate
LiF	Lithium Fluoride
MDR	Medium Dose Rate
MoH	Ministry Of Health
MRI	Magnetic Resonance Imaging
OAR	Organ at Risk
OSLD	Optically Stimulated Luminescence Dosimeters
PDR	Pulsed Dose Rate
PLA	Polylactic Acid
PMMA	Polymethyl Methacrylate
PMT	Photomultiplier Tube

PTV	Planning Target Volume
QA	Quality Assurance
QAP	Quality Assurance Programme
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SPSS	Statistical Package for The Social Science
TCP	Treatment Control Panel
TCS	Treatment Control System
TG-43	Task Group 43
TLD	Thermoluminescence Dosimeter
TPS	Treatment Planning System
TRS-398	Technical Report Series 398
TVL	Tenth Value Layer

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APPENDICES PAGE

KAJIAN DOSIMETRIK APLIKATOR FLETCHER DALAM BRAKITERAPI DENGAN KADAR DOSE TINGGI (HDR) UNTUK KANSER SERVIKS: PENGUKURAN TLD DI DALAM FANTOM AIR PELVIS

ABSTRAK

Latar belakang kajian: intrakavitari brakiterapi yang menggunakan aplikator merupakan kaedah rawatan yang penting untuk kanser serviks dimana salah satu aplikator yang paling banyak digunakan untuk intrakavitari brakiterapi ialah aplikator Fletcher. Untuk memastikan rawatan yang diterima oleh pesikit adalah tepat, pengesahan dos rawatan perlu dilakukan sebelum rawatan. Namun, kajian–kajian yang berkenaan pengesahan dos dalam HDR brakiterapi untuk rawatan kanser seviks yang menilai perbezaan antara dos yang dikira oleh TPS dan dos yang direkod oleh TLD adalah kurang terutamanya kajian yang menggunakan aplikator Fletcher di dalam fantom yang heterogen. **Tujuan kajian**: kajian ini bertujuan untuk menilai tebaran dos dan prestasi dosimetrik yang dihasilkan oleh aplikator Fletcher. **Kaedah kajian**: lapan set TLD yang telah ditentukur menggunakan sumber radionuklid, Iridium-192, diletakan di atas OAR pundi kencing dan rektum di dalam fantom air pelvis yang heterogen dan imbasan CT dilakukan untuk mendapatkan imej untuk TPS. Perancangan rawatan brakiterapi serviks dilakukan untuk mendapatkan dos yang dikira oleh TPS menggunakan 8Gy dose yang ditetapkan. Kemudian, fantom air pelvis diiradiasikan bersama-sama dengan TLD di atas OAR untuk memperoleh dos yang direkod oleh TLD. Perbandingan antara dos yang dikira TPS dan dos yang direkod TLD dilakukan. **Hasil kajian:** dua daripada lapan TLD menunjukkan perbezaan peratusan yang kurang daripada 20% had dos, dengan TLD G6 menunjukkan perbezaan yang terbesar sebanyak 385.72% diantara dos yang dikira TPS dan dos yang direkod TLD. **Konklusi**: hasil kajian menunjukkan perbezaan yang besar antara dos TPS dan dos TLD dalam HDR brakiterapi menggunakan aplikator Fletcher, yang mana hampir

keseluruhan TLD menunjukkan peratusan perbezaan yang lebih daripada had toleransi yang disebabkan oleh beberapa faktor terutamanya posisi aplikator yang salah semasa proses iradiasi berbanding di dalam TPS

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ABSTRACT

Background: Intracavitary brachytherapy has become one of the most important treatments for cervical cancer, along with the use of the applicator during its treatment delivery. The most common applicator used is Fletcher's applicator. To ensure the accurate treatment of brachytherapy, the dose verification of the treatment must be done before the treatment delivery. However, there is a lack of studies on dose verification in cervical cancer brachytherapy that address the discrepancies between the planned dose and the delivered dose using heterogeneous phantoms, especially the one using the Fletcher applicator. **Purpose**: This study aims to assess the dose distribution and dosimetry performance achieved by the Fletcher's applicator and perform dose verification in HDR brachytherapy. **Materials and Method**: The eight sets of thermoluminescence dosimeters (TLD), calibrated using an Iridium-192 source, were placed across the bladder and rectum organ at risk (OAR) inside the heterogenous pelvic water phantom and computed tomography (CT) scanned for image acquisition. The planning of the cervical brachytherapy is done to obtain the calculated TPS dose using the CT image with an 8Gy dose prescription. The phantom is then irradiated along with the TLD to obtain the irradiated TLD-measured dose. The comparison between the TPS calculated dose and the TLD measured dose was done. **Results**: Two of the eight TLD, G2 (5.883%) and G4 (-17.526%), show a dose deviation less than 20% from the TPS calculated dose, while the other six TLD exceed the 20% dose limit, with G9 showing the highest deviation, -278.726% between the calculated and measured dose. **Conclusion**: the result of the study shows significant deviation between TPS calculated dose and the TLD measured dose in HDR brachytherapy using Fletcher's applicator inside heterogenous phantom, with most

percentage different exceeding the acceptable tolerance due to several factor mainly the applicator being mispositioned.

Chapter I

INTRODUCTION

1.1 Background of the Study

Cervical cancer was the fourth most frequent cancer in women, behind breast cancer, colorectal cancer, and lung cancer. The untreated human papillomavirus (HPV) infection of the cervix, which is the lower part of the uterus or womb that exits into the vagina, also known as the birth canal, that may lead to 95% possibility of cervical cancer to occur. Women with human immunodeficiency virus (HIV) are six times more likely than the general population to acquire cervical cancer due to weakened immune systems (Stelzle et al., 2021). Most cervical cancer patients were detected at a late stage due to a lack of information regarding early signs and irregular screenings. The cervical cancer treatment also sometime was delayed due to social barriers, particularly in less resourced countries (Tjokroprawiro B. et al., 2024).

For women with locally advanced cervical cancer, the standard of care has progressed from external beam radiation therapy (EBRT) alone to EBRT plus brachytherapy, and now EBRT plus brachytherapy with concurrent chemotherapy. The use of internal irradiation from brachytherapy offers a high dose to the tumour while sparing the surrounding normal structures. Brachytherapy has been proved as the only technique that providing the high dose required to control cervical cancer (>80 Gy) without producing significant side effects (Benerjee R. and Kamrava N., 2014). HDR Brachytherapy is also increasingly accepted due to various advantages, including being an outpatient treatment, application repeatability, and less radiation exposure for the staff. The cervical brachytherapy technique normally begins with the insertion of an intrauterine tandem vaginal applicator into the patient (Dincer et al., 2024).

The choice of brachytherapy applicators is crucial, and it is determined by the patient's anatomy and the cancer's severity. There are various types of applicators used in HDR brachytherapy, with the Fletcher applicator being one of the most prevalent, particularly in cervical brachytherapy (Mourya A. et al., 2021). The Fletcher's applicator is made up of one long, thin tube that penetrates through the cervix called the tandem and two round, hollow capsules called the ovoid. The Fletcher Suit has a wide range of geometries, including short or long active tandem length in the uterus, several different tandem's angulations, narrow or asymmetric ovoid separation, and varying sagittal levels of the ovoid. The patient's anatomy determines these geometries (Palvolgyi, 2010). As the dose distribution of the brachytherapy source patterns linked with the Fletcher's applicator, it is important to fully understand the applicators characteristic in order to optimise the treatment efficacy and minimise the side effects, as numerous factors and uncertainties can influence dose distribution.

The dose verification of the HDR brachytherapy treatment become the main aim of this study, as dose verification is crucial to the treatment approach since it helps to reduce errors, which leads to more efficient therapy and fewer side effects for the patient. The TPS planning dose should be verified for each clinical use of brachytherapy using an independent method and a less error-prone system. Experimental approaches, such as radiation detectors in solid and liquid phantoms, have traditionally been employed as independent means to validate the accuracy of TPS dose (Jayakody M. et al., 2022).

1.2 Problem Statement

It is crucial to ensure the planned dose is the same as the delivery dose for effective brachytherapy cancer treatment while reducing the dose to healthy tissue. Theoretically, in brachytherapy, the dose delivered to the patient should be the same exact dose as the dose calculated during treatment planning, but because brachytherapy treatment is subjected to uncertainties, there are deviation will be occurs between the planned dose and the delivered

dose. The uncertainties may be due to the different variations in the patient's anatomy, the positioning of the source or applicator during the treatment, or the shift in implant orientation over time (Kirisits C. et al., 2014). In brachytherapy, due to the substantial dose supplied to the target in a single fraction and the OARs dose constraints that must be met simultaneously, it is critical to have as minimal deviation as possible between the planned and delivered doses.

Such deviation may cause several problems that will arise during the radiotherapy treatment, such as the overdosing of healthy tissue, the underdosing of the target tumour, and a decrease in treatment efficiency. Even with the advancement in imaging technique and treatment planning, the deviation will still continue to occur, increasing the toxicity to the patient and decreasing the treatment efficiency (Nikoofar A. et al., 2015). To solve this problem, dose verification is required in order to determine whether the deviation percentage of the dose distribution is within the acceptable level or not.

Furthermore, there is a lack of studies on dose verification in cervical cancer brachytherapy that address the discrepancies between the planned dose and the delivered dose in heterogeneous phantoms, especially the one using the Fletcher applicator. So less information was found about the dosimetric performance and dose distribution pattern of the Fletcher's applicator in the previous study. Hence, the assessment of the dose distribution of HDR brachytherapy using the Fletcher applicator in pelvic water phantom and verification of the dose delivered against the calculated dose in treatment planning is done so it will provide guidance in the future clinical procedure.

1.3 Research Objective

1.3.1 General Objective

To quantitatively assess the dose distribution and dosimetry performance achieved by the Fletcher's applicator and perform the dose verification in the HDR brachytherapy using pelvic water phantom.

1.3.2 Specific Objective

- To calibrate the thermoluminescence dosimeter (TLD) for brachytherapy dose verification using Microselectron HDR brachytherapy suit.
- To determine dose distribution for target coverage and OAR sparing during HDR brachytherapy using fletcher applicator inside the pelvic water phantom
- To determine the deviation between TPS calculated dose and the dose measured using TLD.

1.4 Research Hypothesis

Null hypothesis

- There is no significance difference between dose distribution achieved by Fletcher's applicator between treatment planning and real time measurement using TLD

Alternative hypothesis

- There is significance difference between dose distribution achieved by Fletcher's applicator between treatment planning and real time measurement using TLD

1.5 Significance of the Study

High-dose rate brachytherapy has become increasingly important in cervical cancer treatment, especially when combined with external beam radiotherapy as an adjuvant treatment. Hence, the accuracy and precision of the dosimetry during the treatment of HDR brachytherapy must be performed and it will result significant impact on the treatment outcome and the patient's health. Along with one of the most common applicators used during intracavitary HDR brachytherapy for cervical cancer, Fletcher's applicator, HDR brachytherapy needs careful dose verification in order to make sure that only the intended dose plan is delivered to the patient's tumour to increase the treatment efficiency while preserving the healthy tissue.

One of the key reasons for HDR brachytherapy dose verification is to ensure treatment efficiency by ensuring that the tumour reaches its optimal planned dose while increasing the accuracy of the tumour dose delivery. The dosimetric verification also helps the physicist ensuring the consistency and reliability of the HDR brachytherapy treatment for the patient, where the dose verification become the most crucial aspects of the quality assurance protocols of the brachytherapy. In terms of the role of the Fletcher's applicator in this study, the information on the dosimetric characteristics and dose distribution of the applicator that was analysed in this study can provide feedback for any applicator improvement in design and functionality in order to improve its effectiveness in future intracavitary brachytherapy treatment.

The result of this study on dose verification can provide insightful data that can be used in brachytherapy treatment improvisation while establishing benchmarks and standards that can be used during clinical dose verification across the country in the future. Other than that, the findings of this study can also be used as an educational template for future oncologists or

medical physicists, helping them to understand the pattern of Fletcher's applicator dose distribution and dose verification in brachytherapy and thus help them in their clinical decision-making.

Chapter II

LITERATURE REVIEW

2.1 Cervical Cancer

Based on the HPV Centre's fact sheet (2023), cervical cancer was ranked as the fourth most frequent cancer among women in Malaysia, with about 1700 women diagnosed with the disease and about 100 deaths recorded due to the cancer in 2023. Cervical cancer is a cell cancer that is located inside the cervix, which is a narrow tube below the uterus. There are two types of cervical cancer that may occur inside the cervix's tissue: mostly squamous cell carcinoma (SCC), the cancer cell that starts to develop inside the ectocervix's tissue, and some rare cases of adenocarcinoma, the cancer cell that develops inside the endocervix's glandular cell.

Some cervical tumours may be benign or malignant. Benign masses are mainly known as cell cancers that stay in their initial location without spreading to healthy tissue, while malignant masses spread and metastasize into other normal tissue. Based on the 2023 Federation Internationale de Gynécologie et d'Obstetrique (FIGO) staging of endometrial cancer (Berek et al., 2023), there are four stages of endometrial cancer, with each having three substages. Four main stages were separated via the intensity of the metastases: stage I: the tumour was confined inside the ovary and uterine corpus; stage II: cervical stoma's invasion; stage III: regional and local spread of the tumour; and stage IV: the tumour spread to either the bladder mucosa, intestinal mucosa, or distance metastases. The substages of the FIGO staging was categories with A, B, and C indicators to indicate the severity of the tumour's metastases. It is further explained in the table 2.1.

Table 2.1: The FIGO staging from stage 1 to stage IV (Berek et al., 2023)

Stage	Description
Stage I	Confined to the uterine corpus and ovary‡
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e., low-grade endometroid, with invasion of less than half of myometrium with no or focal LVSI OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary‡
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI§
IC	Aggressive histological types‖ limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI§ of non-aggressive histological types
IIC	Aggressive histological types‖ with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)‡
	IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria
	IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both¶
	IIIC1 Metastasis to the pelvic lymph nodes
	IIIC1i Micrometastasis
	IIIC1ii Macrometastasis
	IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
	IIIC2i Micrometastasis
	IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra-or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

2.2 Radiation Therapy

Radiation can be categorised into two categories: ionising radiation and non-ionising radiation. However, in radiation therapy or radiotherapy, it only applies the use of ionising radiation such as x-ray, gamma ray, radioactive nuclides, and other sources of radiation to destroy the cancer cell by breaking its molecule and causing damaging reactions when they interact with the cells. The main aim of the radiotherapy treatment is to deliver the highest possible radiation dose to the cancer cell and the lowest possible dose of radiation to the healthy surrounding tissue. Based on the Surveillance, Epidemiology, and End Results (SEER) Training (2019) article with title introduction to radiation therapy, it stated that radiation therapy can also be divided into two types: external beam radiation therapy and internal beam radiation therapy. External beam radiation therapy generally delivers the radiation from a distant source located outside the patient's body to their tumour, such as a photon beam, an electron beam from a linear accelerator, and gamma rays from a Cobalt-60 machine. Internal

radiation therapy, on the other hand, delivers the radiation from inside the patient via the insertion of a source inside the applicator, catheter, or seed. This method is mainly known as brachytherapy, where a radioactive source is transferred into or near the tumour site of the patient and irradiated. Sometimes, radiation therapy will act as the main treatment for the cancer, but for some specific cancers, it will act as an adjuvant treatment, where it is done to avoid recurrence of the cancer after the other main treatment is done.

2.3 HDR Brachytherapy

There are several classifications of brachytherapy in terms of type of implant, dose rate, treatment duration, and loading pattern (Thakur S., 2018). For the type of implant, there are five types that are usually applied in modern brachytherapy: intracavitary, interstitial, intraluminal, intravascular, and surface mould. Each has a different delivery technique depending on the specific organs of the treatment. For dose rate, there are four levels of dose rate available: low dose rate, (LDR) ranging between 0.4–2Gy/hr, medium dose rate (MDR), ranging between 2–12Gy/hr, high dose rate (HDR) where dose rate>12Gy/hr, and pulsed dose rate (PDR). The treatment duration of brachytherapy consists of permanent implantation, mainly in a radioactive seed implant, and temporary irradiation, such as in intracavitary and interstitial brachytherapy. The last classification is the source loading pattern, which consists of preloading and afterloading. The source is loaded inside the applicator before being placed into the patient in preloading, while in afterloading, the applicator is inserted first into the patient and then the source is inserted next using two main methods: manual afterload (source transferred manually by forceps) and remote afterload (source insert by motor-driven transport system).

Based on the study by Kollmeier M. et al. (2022), the comparison between LDR (Palladium-103 seed) and HDR (Iridium-192) brachytherapy combined with external beam

radiotherapy was studied in terms of toxicity among 90 prostate cancer patients. The results of the study show that there is less genitourinary toxicity in the HDR brachytherapy cohort compared to the LDR cohort. This indicates that HDR is a more ideal dose rate for current brachytherapy than LDR. Due to this reason, the investigation of HDR brachytherapy was the main focus in this study. Furthermore. The study also used intracavitary implant technique and applied the applicator usage.

2.3.1 Brachytherapy Treatment Delivery

Even though there are many implant types of brachytherapy, this study will focus on intracavitary brachytherapy as it is suitable for organs with cavities, such as the cervix, which align with the main aim of this study to assess the dosimetric characteristics. Procedurally, intracavitary brachytherapy will start with the applicator implantation procedure, where a suitable technique and applicator are chosen depending on the patient tumour location, size, and OARs involved. Then the patient with the inserted applicator undergoes an image acquisition process using a computed tomography (CT) scan or magnetic resonance imaging (MRI) to obtain the image data for treatment planning inside treatment planning system (TPS). Quality assurance (QA) of brachytherapy machine and lastly the brachytherapy treatment delivery

2.3.2 Brachytherapy source

In this modern brachytherapy advancement, the Iridium-192 is considered the golden standard in brachytherapy clinical practice due to its high specific activity, which is 380keV, and its short half-life, which is 74 days. However, due to its low half-life, some institutions prefer the usage of Cobalt-60 due to its advantages of having a longer half-life, which is arounds 5.27 years, where the replacement of the source is not frequent. As a disadvantage of Cobalt-60, the radionuclides have higher specific activity than the Iridium-192 source, which

is 1.25MeV, and this is the reason of the Cobalt-60 source has higher toxicity, therefore requires more shielding than the Iridium-192 source. For example, in concrete shielding, about 210mm of thickness is required to shield the Cobalt-60 compared to the Iridium-192 source, which required 139mm of thickness of concrete based on the equilibrium of the tenth value layer, TVL As for the physical aspect of the source, Iridium-192 can be produced in small size, allowing the source to fit inside the interstitial brachytherapy catheter, resulting in the widespread use of Iridium-192 as a source in HDR brachytherapy (Tantivatana T., 2018).

2.3.3 Brachytherapy Quality Assurance

Based on the requirements of Malaysian Ministry of Health (MoH), the Quality Assurance Programme (QAP) is essential for the government and private radiotherapy departments to maintain its quality and performance. As well as linear accelerators, brachytherapy also needs to undergo quality assurance testing for its HDR remote afterloading machine. Some important test involved before the HDR brachytherapy treatment is source positioning test and source strength calibration test. The routine positioning test is vital and recommended as a mandatory test before the treatment because the brachytherapy treatment is associated with a physically small sized source where several spacial factors, such as its need to be close to the tumour, its steep dose falloff, and its high inverse square correction, are required to be taken into account (Awunor O., 2018). The test was conducted using the source positioning checking tool connecting to the HDR brachytherapy machine through transfer tubes to verify the source location with the specific dwell position should be within ±1mm based on American Association of Physicist in Medicine, AAPM, Task Group 40, TG40 (Kutcher et al., 1994) or ±2mm based on AAPM TG56 and European Society for Radiotherapy and Oncology, ESTRO Report no. 8 (Rodrigues A. et al., 2022).

2.3.4 Brachytherapy Treatment Planning

Brachytherapy treatment planning required the used of image acquisition from the patient with applicator or catheter inserted. There are already many developed software or treatment planning system that assist the treatment planning process. However, when it's come to the brachytherapy treatment planning, Oncentra software developed by Elekta came out on top of the list. The software's create the workflow of the brachytherapy procedure along with its multiple useful tools that help each planning step such as the contouring, catheter reconstruction, activation of dwell position, normalization, optimization and prescription as well as fast dose calculation of the plan along with the Dose Volume Histogram (DVH) analysis (Yang J. 2018). In contouring process, the delineation of the target volume and critical organ such as bladder and rectum was done by the planner and source path is reconstructed using catheter reconstruction tools. The dose point optimisation was done, which then followed by graphical optimisation. Using the graphical optimisation tool, additional optimisation was carried out by manually dragging isodose lines. On the target volume, dosage points were generated at a 5 mm interspace distance in order to normalise the specified dose of 6Gy per fraction (Anbumani S. et al., 2014).

Several plan evaluations, such as the conformity index (CI) and homogeneity index (HI), are common practices in many institutions before the radiotherapy plan is delivered. The calculation of the CI is to estimate the coverage of the dose distribution inside the planning target volume, and the HI is to assess the dose volume homogeneity for the implant (Prabhakar R., 2010). Other than that, Due to the recommendation by Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) and American brachytherapy society (ABS), the calculation of $D_{0.1CC}$, D_{1CC}, and D_{2CC} doses to OARs such as the bladder, sigmoid, and rectum, this should be done for every gynaecological brachytherapy

plan. According to ABS guidelines, the D2cc for the rectum and sigmoid should be less than 70 to 75Gy, while the D2cc for the bladder should be less than 90Gy.

2.4 Cervical Brachytherapy Applicator

In cervical cancer treatment, the choice of brachytherapy applicators is crucial, and it depends on the patient's anatomy and the disease's severity. Additionally, the imaging modalities to be utilised for applicator reconstruction and treatment planning are taken into consideration while choosing the applicators. Due to the evolution of applicator usage in gynaecological brachytherapy, these primary practices acknowledged the use of ionising radiation in medicine, and medical professionals created their own protocols for treating cervical cancer. Because different clinicians provided different treatments, the Stockholm, Paris, and Manchester systems developed. Each of these systems has its own unique dose prescription, activity distribution principles, and applicator design (Mourya A. et al., 2021). There are many types of existing applications, and they will be more based on their development and evolution in the future.

2.4.1 Fletcher Suit Applicator

The Fletcher Suit Applicator consists of one long, thin tube that passes through the cervix called the tandem and two circular, hollow capsules called the ovoid. Compared to the Utrecht applicator, fletcher applicator did not have hole for the needle to be placed throughout the ovoid. The tandem part of the applicator angulation can be changed into the tandem with angulation typically 15°, 30°, and 45° angles depending on the patient anatomy. The distance between two ovoids can be adjusted and called ovoid separation, which may impact the overall dose distribution of the applicator. There is a wide range of Fletcher Suit's geometries, including: short or lengthy active tandem length in the uterus; narrow or asymmetric ovoid separation; and varied sagittal levels of the ovoids. These geometries are decided based on the

anatomy of the patient (Palvolgyi J., 2010). Some applicators used tungsten to reduce the dose to the bladder and rectum. The image 2.1 show the Fletcher's applicator made out of CT/MRI compatible material.

Figure 2.1 of computed tomography/magnetic resonance (CT/MR) compatible Fetcher's Applicator by Nucletron (Elekta, 2012)

The study from Bonifaz A. et al. (2024) conducted a retrospective study between two different applicator, Fletcher-Suit-Delcros Tandem and Ovoid with the Syed-Neblett applicator, to investigate the dosimetric and toxicity comparison of two applicator. The study analysed the dosimetric parameters of target volume and OARs, along with the toxicity that was reviewed using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Based on the result, the D_{2CC} for bladder, small bowel, and sigmoid in the Syed-Neblett applicator is lower, but patients have a higher chance of developing late toxicities compared to the tandem and ovoid.

2.5 TG-43 Dose Calculation

The AAPM TG-43 published guidelines for the dosimetry of interstitial brachytherapy sources in 1995. The research of AAPM TG-43 is known as the most used formalism for calculating dose distribution around brachytherapy sources, and the described formalism is

used in many TPSs. It proposed that a new dosage formalism based on measurable quantities be implemented. According to the paper, the dose distribution around brachytherapy sources is calculated using a number of variables obtained from measurement or Monte Carlo simulation methods in a uniform phantom (Mozaffari & Ghorbani, 2019).

The modular structure enables the computation of doses in two dimensions for Pd-103, 1-125, and Ir-192 sources. According to the TG-43 report for brachytherapy sources, dose distribution can be calculated using a polar coordinate system with the origin at the middle of the source, as illustrated in Figure 2.2.

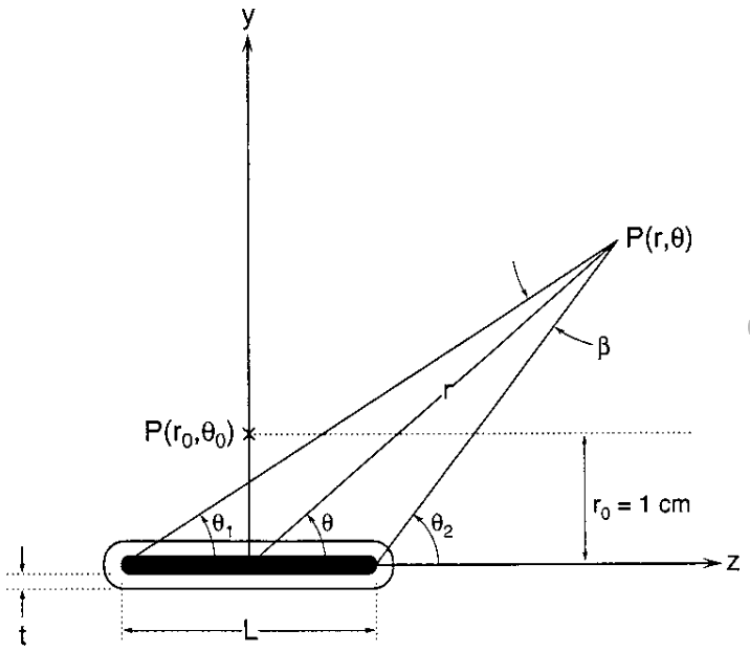

Figure 2.2 shows illustration of TG-43 dose formalism for brachytherapy source (Nath R. et al., 1999)

This formalism defines the point of interest as P (r, θ), with r representing the distance from the point to the origin and θ representing the polar angle. The reference point is P (r, θ), where r_0 is the distance from the origin to the point of interest, which is 1 cm, and θ is the angle with regard to the source's long axis, which is π/2 as the reference coordinate. As a result, this equation 2.1, yields the dosage rate at the position P (r, θ) in water.

$$D(r,\theta) = S_K \cdot \Lambda \cdot \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \cdot \ g_L(r) \cdot F(r,\theta) \qquad \text{…Equation 2.1}$$

In the equation, r is the distance (cm) between the origin and the place of interest. In the equation, P = θ, where θ is the angle between the radius vector r and the source's long axis, θ_0 is the source's transverse plane (equal to π/2 radians), S_k is the air kerma strength, Λ is the dose rate constant, G(r, θ) is the geometry function, is the radial dose function, and F(r, θ) is the anisotropy function. P(r_0, θ_0) is defined at r=1 cm and θ = 90° (Ab Shukor N.S. et al., 2022)

2.6 Pelvic Phantom in Brachytherapy Research

Many research studies developed their own water phantoms for their studies in radiotherapy. The study by Jayamani J. et al. (2023) used heterogeneous phantoms of male pelvis for treatment verification in patient-specific quality assurance of IMRT. The shells of the phantom housing were made out of polymethyl methacrylate (PMMA) and reconstructed in an octagon shape. The phantom was then filled with water to represent the human tissue. Inside the phantom, there is the holder or rod made out of the PMMA that will attach the OAR together in their specific position.

There is other study by Kut C. et al. (2022) where the gynaecological phantom was created with positive moulds from 3D printing and polyvinyl chloride (PVC) plastisol. Tissue texture/acoustic qualities were recreated with varying plastic softener/hardener ratios and microbead densities. The HU number for the patient tissue and the phantom is determined and compared. As for the result, the data collected from the study is show that the phantom is compatible with the multimodality imaging and can be seen using the ultrasound.

2.6.1 Tumour and OARs Replication and Refer Points

The study from Jayamani J. et al. (2023) uses different material to substitute the OAR inside the phantom and represent the actual organs inside the human body. So the material and

its density in the OAR supposedly have the same value as the organ's density. In their study, the The electron density and CT number of each OAR was analysed and compared with actual organ electron density and CT number using specified software. In her study, the bladder and rectum OAR were made out of polyethene, and the prostate OAR was made from nylon. The materials of the phantom and OAR were based on the International Commission on Radiation Unit and Measurement (ICRU) Report No. 37.

Another study on brachytherapy dose verification by Nikofaar A. et al. (2015) is on the anthropomorphic phantom that was constructed using natural bone and a mixture of paraffin and sodium chloride to imitate human tissue. The lung inside the anthropomorphic phantom was imitated by using the sponges. Plus, there is a pathway for the oesophagus applicator extending from the throat region to the treatment area. The TLDs are placed across several OARs and categorised into two regions: those far from the target at the suprasternal notch (>16 cm) and those close to the target (<16 cm).

2.7 In vivo Dosimetry for HDR Brachytherapy inside Phantom

The HDR brachytherapy has proven to have a steep dose fall and extremely high inverse square correction, which is probably one of the reasons why proper and careful dose verification is important to recheck the TPS's planned dose distribution (Jayakody M. et al., 2022). One of the independent methods of dose verification that is often used in most health institutions is in vivo dosimetry. It is a measurement of radiation dose within the radiotherapy patient that was done using in vivo dosimeters such as thermoluminescence dosimeter (TLD) and the semiconductor diode.

The study by Lambert J. et al. (2007) explained the requirements of the dosimeters in brachytherapy dosimetry, which include that the dosimeter must be small in size, capable of being located near the organ that will be treated, and have high sensitivity to radiation. The

Lambert J. et al study will provide guidance on the selection of the suitable dosimeter in this study.

In addition, Malekie S. et al. (2024) study focused on developing and manufacturing a phantom for quality control of high-dose rate Cobalt-60 sources used in gynecologic brachytherapy. Using 3D printing technology, a phantom composed of polylactic acid (PLA) with a density of 1.24 g/cm3 was created and fabricated in SSDL. This phantom, which has dimensions of 15 x 15 x 15 cm3, was filled with distilled water. Subsequently, the embedded holder was used to hold the EBT3 radiochromic films while the study's EBT3 film calibration and dose difference were being determined.

2.7.1 Thermoluminescence dosimeter (TLD)

TLD capabilities of detecting the radiation dose and flexible shape and form makes TLD used extensively for the in vivo dosimetry in brachytherapy. Initially, the TLD will be annealed before it was irradiated to remove the remaining reading residue from the previous irradiation. The detector consist of valence band and conduction band. During the irradiation process as shown in the figure 2.3, electron on the valence band will excite to the conduction band when in contact with ionising radiation and trapped inside it. When the TLD is heated as shown in figure 2.4, the light will be emitted and the trapped electron will be release from conduction band. The emitted light is the TLD dose reading.

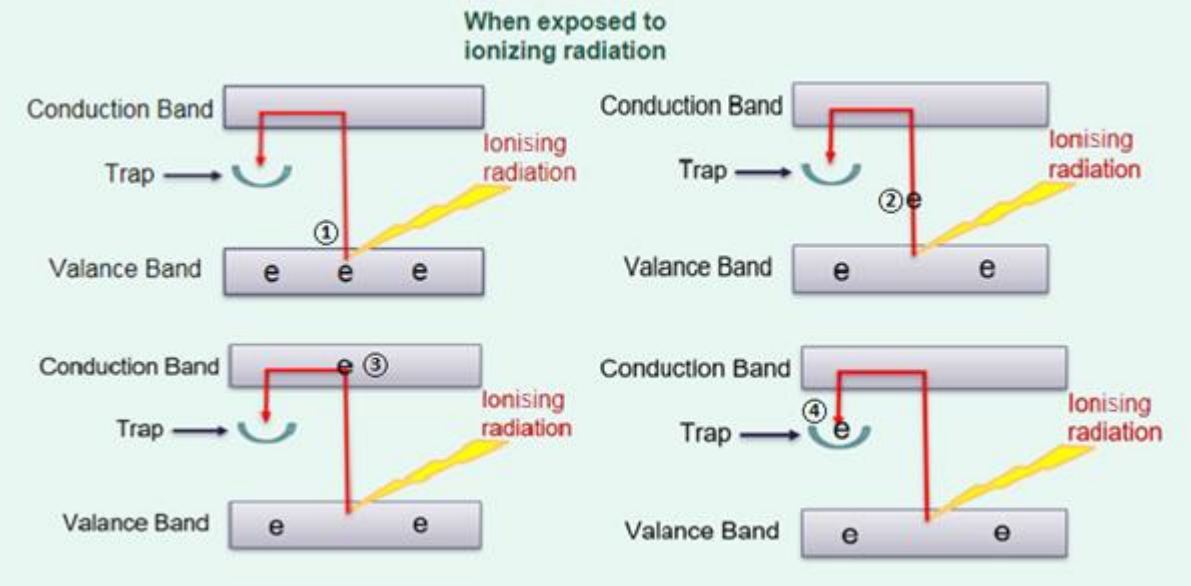

Figure 2.3 show the working principle of TLD that involve the electron shift between valence band and conduction band when exposed to the ionising radiation

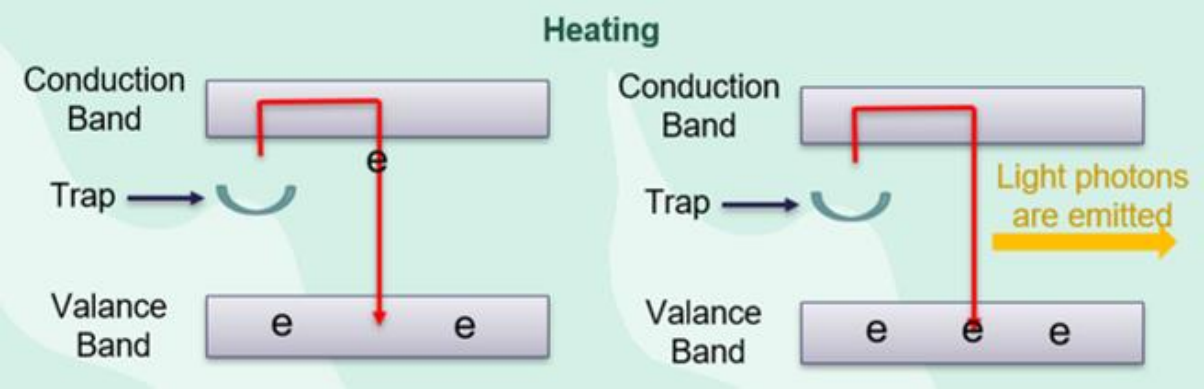

Figure 2.4 show the working principle of TLD that involve the electron shift between valence band and conduction band during its reading/heating

Due to TLD required to be anneal and read, the TLD is not the real time dose measurement dosimeter as the post irradiation and pre irradiation process may take about 25 hours to completed (Lambert J. et al., 2007). Most phantom research employ TLDs for point dose assessments. As a result, the measured dose may not always accurately reflect the clinically meaningful dose to the OARs. One disadvantage of utilising them as dosimeters is

the need for repeated measurements at many point on the dosimeter to accurately determine the dose received by OARs (Jayakody M. et al., 2022).

2.7.2 TLD Calibration using Ir-192 source

TLD calibration requires the proper calibration in order to keep it in its optimum condition to accurately assess the dosage received by the patient and to ensure radiotherapy efficiency. Based on Haworth A. et al., (2013) The TLD calibration is commonly performed using Cobalt-60, as the source is easily accessible, or a megavoltage source, as it has a pre-established dosimetry standard or formalism such as the one stated in International Atomic Energy Agency, IAEA's Technical Report Series 398 (TRS-398) and AAPM 51. On the other hand, the Iridium-192 source is commonly used in HDR brachytherapy after loader, and the calibration using the source requires careful geometrical consideration due to the significant dose gradients surrounding the source. Plus, as the absorbed dose-to-water primary standards for Iridium-192 are still being developed, there is still no standard formalism for measuring absorbed dosage from the Iridium-192 source that will assist the TLD calibration process (Haworth A. et al., 2013).

In the same study of TLD calibration by Haworth A. et al. (2013), there was a comparison between TLD calibration with irradiation in air, irradiation in water, and irradiation in the modified non-homogenous phantom and another method of TLD calibration using a linear accelerator. The cross-calibration with the ionisation chamber is done with the TLD calibration for each calibration method. Based on the result, the average measured dose to the centre is 4% higher for air calibration, 1% higher for water calibration, 1.5% lower for modified phantom, and 6% higher for linear accelerator calibration than the prescribed dose. From the result, it's concluded that the calibration of TLD inside the water or water-equivalent phantom had the lowest deviation from the prescribed dose and was superior compared to the other

method. Thus, the calibration of the TLD using Iridium-192 should be conducted inside the water or water-equivalent phantom.

As for the TLD calibration result analysis, most of the studies calculated the standard deviation, coefficient of variance, and individual TLD sensitivity correction factor, Si=Ri/Ravg, using TLD. It is due to the reproducibility test and sensitivity test, which correlate with the coefficient of variance and individual TLD sensitivity correction factor, respectively. The research by (D'Avino et al., 2020) used the same method and determined the selection of TLD that will be used inside the study based on the sensitivity test during the TLD calibration. From the study, the TLDs that have lower Si than 0.9 will be considered TLDs with low sensitivity and excluded from the irradiation. The 0.9 threshold limit of the TLD sensitivity can be applied in the study as well to only use TLDs with optimum sensitivity in the study to achieve an effective result.

2.8 Treatment/Dose Verification and Data Analysis

The dose verification of the HDR brachytherapy treatment become the third objective of the study, as dose verification is crucial to the treatment approach since it helps to reduce errors, which leads to more efficient therapy and fewer side effects for the patient. Most of the study uses experimental approaches, such as radiation detectors in solid and liquid phantoms, to validate dose delivered to the patient to determine the accuracy of TPS dosage estimates.

There are various other dosimeter used during the dose verification of brachytherapy. The study by Nikofaar A. et al. (2015) on dose verification of intraluminal brachytherapy on the anthromorphic phantom for 23cm^3 volume of target at upper esophagus with multiple reference point at eye, thyroid, submandibular gland, sternum, spine and parotid using TLD in HDR brachytherapy research with Iridium-192 as source. Based on the result, deviation of the measured dose is 7% different from the prescribed dose. So they concluded from the study that

the TLDs can successfully be incorporated into the in vivo brachytherapy dose verification experiments.

In order to validate the TPS algorithms employed in HDR brachytherapy, a heterogeneous phantom was created in the second study by Moura et al. (2015) utilising Virtual WaterTM (VM), BR50/50TM, cork, and aluminium organised in 11 heterogeneity configurations. Several types of dosimeters are used in the study to compare the capabilities of performing dose verification, such as TLD-100, Gafchromic EBT3 film, an ExradinTM A1SL IC, MC code, and TPS. However, in contrast to the EBT3 film, TLD and IC films, on the other hand, have demonstrated minor (<0.5%) deviations from the TPS estimations. When low-density materials are used in the homogenous phantom, EBT3 films are more vulnerable than other dosimeters used in this work. Since the energy-dependent nature of the EBT3 films depends on the thickness of the material and the composition of the medium, the uncertainty of EBT3 is higher than TLDs and ICs.

Other than dose verification, the method of the data analysis that was done in the previous study was also reviewed, where most of the study used statistical analysis to determine its result based on accepting or rejecting the null hypothesis. A study by Moonkum N. et al. (2023) analysed their in vivo dosimetric data between dose measured by a diode rectal dosimeter and dose calculated by TPS using a parametric and paired t test, as the data sample obtained from the study is normal. In addition, the study by Chaikh A. et al. (2014) determined the suitable statistical test for every comparison that was done in the dosimetry of radiotherapy. From his study results, the proposed tests that are suitable for radiotherapy dosimetric comparison are the standard t-test, Wilcoxon signed-rank test, analysis of variance (ANOVA), and Friedman ANOVA.

Chapter III

MATERIALS AND METHOD

3.1 Materials

3.1.1 Thermoluminescence Dosimeter (TLD)

The dosimeter that was used in the study is the thermoluminescence dosimeter (TLD), Harshaw, USA. The dosimeter requires proper calibration to ensure the reading recorded by the dosimeter is reliable. The ten chips of TLDs were used to record the charge measured from the brachytherapy source during the calibration process and eight chips of TLDs were used inside the data collection process. Among the types of TLDs used during the study, the TLD100 is used, which is usually made out of lithium fluoride (LiF) doped with magnesium (Mg) and titanium (Ti), becoming LiF:Mg,Ti, which is the TLD type that was used in this study. The dosimeter comes in variable shapes and sizes; it is available in rod, chip, powder, etc.; however, in this study, a flat chip with dimensions of 3mm × 3mm × 1mm was used. Plus, to avoid TLDs receiving readings from CT scanning, eight dummy TLDs were used to mark the location of the actual TLD during CT image acquisition, thus allowing TLD localization inside the treatment planning system. The dummy has the same specifications as the actual TLD but has several defects, such as being oxygenised or rusted.

3.1.2 TLD Annealing Oven, Annealing Plate and Thermosoft Software

As one of the advantages of TLD is that it can be reused again, the process of clearing the previous reading is required, which is the annealing process of TLD. The materials used in this process include the annealing plate, TLD Annealing Oven TLDO, and Thermosoft software. The annealing plate made out of a steel is an accessory that comes with the TLD

Annealing Oven and consists of 120 slots that were used to store the TLD as shown in the figure 3.1 (right) during the annealing process inside the oven. The main machine, the TLD Oven TLDO as shown in the figure 3.1 (left) developed by RADpro International GmbH, Germany, was used to anneal the TLD100 in this study. The oven was created for thermoluminescence dosimetry and is managed by a microprocessor that may be programmed. The pre-heating programme and the annealing programme are the two standard programmes included with the oven model. While the preheating programme is completed before the reading TLD, annealing is done prior to TLD irradiation. Since the TLD preheating process was not carried out inside this machine, only the annealing programme was used in this research. During the annealing process, the selected heating profile of TLD100 is set in the Thermosoft software, developed by the Thermosoft International Corporation, United State of America, to keep track of the heating, avoid overheating of the TLDs, and shows the heating profile of the TLD as in Appendix 1.

Figure 3.1 of TLD annealing oven (left) and the TLD inside the annealing plate (right)