DOSIMETRIC ANALYSIS OF STANDARD TANDEM PLUS RING APPLICATOR IN HIGH DOSE RATE (HDR) BRACHYTHERAPY FOR CERVICAL CANCER: TLD MEASUREMENT IN PHANTOM

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UNIVERSITI SAINS MALAYSIA

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by

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Dissertation submitted in partial fulfilment
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CERTIFICATE

This is to certify that the dissertation entitled 'Dosimetry Analysis of Standard Tandem Plus Ring Applicator in High Dose Rate (HDR) Brachytherapy for Cervical Cancer: TLD Measurement in Phantom' is the bona-fide record of research work done by Hazrul Haniff Bin Hamsir (150143) 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.

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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 Univeristi Sains Malaysia the right to use the dissertation for educational or further research purposes.

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LIST OF ABBREVIATIONS

AAPM	American Association of Physicists in Medicine
ASEAN	Association of Southeast Asian Nations
BT	Brachytherapy
CF	Calibration Factor
CI	Conformality Index
CT	Computed Tomography
CV	Coefficient of Variation
DTLD	Dose measured by TLD
DTPS	Dose calculated by TPS
DVH	Dose Volume Histogram
EBRT	External Beam Radiotherapy
FIGO	Federation of Gynaecology and Obstetrics
FOV	Field of view
GTV	Gross Tumour Volume
HDR	High Dose Rate
HRCTV	High Risk Clinical Target Volume
IAEA	International Atomic Energy Agency
ICBT	Intracavitary Brachytherapy
ICRU	International Commission on Radiation Units and Measurements
IGBT	Image-guided Brachytherapy
IPSA	Inverse Planning Simulated Annealing
LDR	Low Dose Rate
LET	Linear Energy Transfer
LINAC	Linear Accelerator
MDR	Medium Dose Rate
MRI	Magnetic Resonance Imaging
MV	Megavoltage
OARs	Organs at risks

PDR	Pulse Dose Rate
PMMA	Polymethyl Methacrylate
PMT	Photomultiplier tube
QA	Quality Assurance
QC	Quality Control
RAKR	Reference Air Kerma Rate
RLR	Reference Light Reading
RTOG	Radiation Therapy Oncology Group
SD	Standard Deviation
TCP	Treatment Control Panel
TCS	Treatment Control System
TG-43	Task Group-43
TLD	Thermoluminescence Dosimeter
TO	Tandem and Ovoid
TPS	Treatment Planning System
TR	Tandem and Ring
TTP	Time Temperature Profile
TU	Treatment Unit
UI	Uniformity Index
WHO	World Health Organisation

LIST OF SYMBOLS

%	Percentage
≤	Equal or less than
C	Coulomb
cm^3	Centimetre cubic
$D_{X\%}$	Dose received by X percent volume of a structure
D_{Xcc}	Dose received by X cm^3 volume of a structure
Gy	Gray
$V_{X\%}$	Volume of structure received X percent of prescribed dose
μ	Micro

ANALISIS DOSIMETRIK APLIKATOR "STANDARD TANDEM PLUS RING" DALAM BRAKITERAPI KADAR DOS TINGGI (HDR) UNTUK KANSER SERVIK: PENGUKURAN TLD DALAM PHANTOM

ABSTRAK

Latar Belakang: Aplikator "Standard Tandem Plus Ring" adalah salah satu aplikator yang popular digunakan dalam brakiterapi intrakavitari untuk kanser serviks. Ini disebabkan oleh geometri aplikator ini yang mudah digunakan dan boleh dihasilkan semula. Walau bagaimanapun, pemahaman yang menyeluruh mengenai tingkah laku dosimetrik aplikator ini diperlukan untuk meningkatkan keberkesanan rawatan dan mengurangkan ketoksikan kepada organ berisiko (OARs). **Tujuan:** Kajian ini bertujuan untuk menilai tingkah laku dosimetrik berkaitan dengan aplikator "Standard Tandem Plus Ring" dan melakukan verifikasi dos pelan rawatan untuk brakiterapi HDR kanser serviks. **Kaedah:** Sebuah aplikator "Standard Tandem Plus Ring" dipasang di dalam phantom pelvis wanita heterogen dengan cip dosimeter termoluminesens (TLD-100) diletakkan pada OARs. Imej Tomografi Berkomputer (CT) bagi phantom diambil, dan pelan rawatan dibuat dengan dos 7 Gy ditetapkan kepada tumor. Organ yang berisiko dipastikan menerima dos dalam had toleransi iaitu 6.5 Gy untuk pundi kencing dan5.5 Gy untuk rectum. Lapan titik dos dicatatkan dalam sistem pelan rawatan (TPS), dan ia dibandingkan dengan dos yang diukur oleh cip TLD-100 semasa penyinaran phantom. **Keputusan:** Corak pengedaran dos berbentuk pear diperoleh, dan dos yang diterima oleh 2 cm^3 (D_{2cc}) pundi kencing dan rektum masing-masing adalah 1.767 Gy dan 5.412 Gy. Daripada 8 titik dos, 7 titik mempunyai peratusan sisihan kurang daripada 20% manakala 1 titik pada rektum mempunyai sisihan 20.864% antara dos yang dikira dan diukur. **Kesimpulan:** Perbezaan peratusan antara DTPS dan DTLD pada titik

pengukuran mempunyai persetujuan dalam ±20%. Sementara itu, pada titik pengurkuran lain yang mempunyai peratusan sisihan lebih daripada ±20% adalah disebabkan oleh had individu dosimeter itu sendiri.

DOSIMETRIC ANALYSIS OF STANDARD TANDEM PLUS RING APPLICATOR IN HIGH DOSE RATE (HDR) BRACHYTHERAPY FOR CERVICAL CANCER: TLD MEASUREMENT IN PHANTOM

ABSTRACT

Background: Standard Tandem Plus Ring applicator is one of the popular applicators utilised in intracavitary brachytherapy for cervical cancer. This is due to its geometry that easy to be employed and reproducible. However, a comprehensive understanding on the dosimetric behaviour of these applicator is required to improve the treatment efficacy and minimise organ at risks (OARs) toxicities. **Purpose:** This study aims to evaluate the dosimetric behaviour associated with the Standard Tandem Plus Ring applicator and to do a dose verification of the treatment plan for cervical cancer HDR brachytherapy. **Methods:** A Standard Tandem Plus Ring applicator was assembled in a heterogenous female pelvic phantom with thermoluminescence dosimeter (TLD-100) chips attached on the OARs. Computed Tomography (CT) images of the phantom was acquired, and treatment plan was created with 7 Gy dose prescribed to the tumour points. The OARs were ensured to receive dose within the tolerance which 6.5 Gy for bladder and 5.5 Gy for rectum. Eight dose points were noted in the treatment plan system (TPS), and they were compared with the dose measured by the TLD-100 chips during the phantom irradiation. **Results:** A pear-shaped dose distribution pattern was obtained, and dose received by 2 cm^3 (D_{2cc}) of the bladder and rectum were 1.767 Gy and 5.412 Gy respectively. Out of 8 dose points, 6 points have percentage deviation less than 20% while 2 points (E2 and E7) have deviation -23.133% and -24.222% between calculated and measured dose respectively. **Conclusion:** The percentage difference between DTPS and DTLD at the points of measurement have agreement within ±20%.

Meanwhile, other points that have percentage deviation more than ±20% were due to individual limitation of the dosimeters itself.

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Cervical cancer is one of the leading causes of morbidity and mortality among women worldwide. In Malaysia, it is now statistically recorded become the third most frequent and the fourth most lethal cancer among women. (WHO, 2021). Despite being the cancer with the largest documented potential for secondary prevention, this illness is extremely curable at a minimal risk and inexpensive when screening of asymptomatic women is combined with adequate diagnosis, treatment, and follow-up.

The clinical guidelines for the management of cervical cancer have been published by several reports. In general, the reports agree that the choices of treatment course for cervical cancer include surgery (hysterectomy), chemotherapy, and radiation therapy (radiotherapy) suitable to the classification and staging of the cancer. (Rosenblatt & International Atomic Energy Agency, 2013, Ministry of Health Malaysia, 2015, Health Commission of the PRC, 2022).

Brachytherapy (BT) is a type of internal radiation therapy that plays a crucial role in the management of cervical cancer. It delivers high doses of radiation directly to the tumour using a sealed radiation source. BT can be divided into several categories according to the dose rate of the source, and the high dose rate (HDR) brachytherapy is the most commonly used brachytherapy technique nowadays. This is owing to its practicality, curative effect, and safety aspects. (Sonali *et al.* 2015 and Chino *et al.* 2020).

The standard tandem and ring applicator method represents a widely used approach in cervical cancer brachytherapy. This method involves the insertion of a tandem within the intrauterine cavity and a ring applicator around or on either side of cervix (lateral fornixes) to deliver radiation. While this technique has demonstrated the ability to produce a desired result of treatment, variations in dose distribution patterns can occur. Thus, impacting treatment outcomes and potential toxicities to the other healthy organs (Banerjee & Kamrava, 2014).

Understanding the dose distribution patterns associated with the standard tandem and ring applicator is important for optimising treatment efficacy and minimising adverse effects, as various factors, and uncertainties can influence the dose distribution. This is because obtaining the optimal dose distribution requires several steps which is dose calculation inside treatment planning system (TPS) and pre-treatment quality assurance method to verify the dose calculated.

Ultimately, a method of dose verification in brachytherapy is essential to quantify the dosimetric accuracy of treatment plan, identify potential sources of discrepancies through the differences between planned dose and measured dose and justify the reliability of treatment plan system to be applied in a clinical setup. (Kertzscher *et al.*, 2014). This encompasses diverse methodologies including experimental measurements. Thus, a comprehensive dosimetry analysis is essential to assess the adequacy of radiation deliver to the tumour area and ensure sparing of critical organs at risks (OARs).

1.2 Problem Statement

There are several factors that can influence the brachytherapy treatment outcome. This includes the specific model used for source distribution in target area and the algorithm used to calculate dose distribution (Suntharalingam, Podgorsak & Tolli, 2006). These aspects must be carefully investigated due to the uncertainties that might occur during dose calculation and treatment delivery workflow. Uncertainties related to the dose calculation stem partly from flaws in the dose calculation protocol. Current TPS incorporates the American Association of Physicists in Medicine Task Group (TG)-43 formalism considers that a patient is composed of water. Thus, it ignores tissue heterogeneity of a real human body (Kertzscher *et al.*, 2014). In addition, clinical uncertainties such as applicator and organ displacements can impact treatment outcomes, as organ-applicator movements can occur during imaging and treatment (Tanderup *et al.*, 2013)**.**

To distinguish all of these aspects, dose verification prior to treatment delivery is needed. There are critical challenges in verifying the actual dose delivered against the planned dose because unlike external beam radiotherapy (EBRT), dose verification in brachytherapy is challenging due to the steep dose gradient (Kertzscher *et al.*, 2014). The current state of understanding the dose distribution patterns associated with particular model employed in brachytherapy and dose verification method is limited. Thus, further study is needed to address this gap. Existing studies often lack the granularity necessary to capture the complexities of the dose distribution, particularly in regions close to critical organs. Consequently, there is a risk of overexposure to healthy tissues or undertreatment of the target volume, which can impact the treatment outcome.

Establishing evidence-based procedures using specific applicator configuration is crucial for achieving consistent and improved treatment outcomes in brachytherapy. This research seeks to address these challenges by investigating dose distribution patterns for cervical cancer brachytherapy with the utilisation of standard tandem plus ring applicator and to verify the accuracy of the treatment planning system to calculate the dose distribution. The ultimate objective is to enhance the accuracy of radiation administration, minimising the risk of complications of OARs and improving the therapeutic outcome for cervical cancer treatment.

1.3 Research Objective

1.3.1 General Objective

To evaluate the dosimetric behaviour associated with standard tandem plus ring applicator and do a dose verification of the treatment plan for HDR brachytherapy for cervical cancer treatment.

1.3.2 Specific Objectives

I. To calibrate the TLD dosimetry system for HDR brachytherapy treatment plan dose verification using Iridium-192 source.
II. To assess the dose distribution pattern produced by standard tandem plus ring applicator in terms of target coverage and critical organs sparring using TLD dosimetry system inside heterogenous female pelvic phantom.
III. To validate the dose calculated by the treatment planning system using TLD dosimetry system for the HDR brachytherapy for cervical cancer treatment.

1.4 Research Hypothesis

I. Null Hypothesis:

There is no significance difference between the dose distribution calculated by the treatment planning system (TPS) and dose measured by the TLD dosimetry system when associated with the usage of standard tandem plus ring applicator.

II. Alternative Hypothesis:

There is significance difference between the dose distribution calculated by the treatment planning system (TPS) and dose measured by the TLD dosimetry system when associated with the usage of standard tandem plus ring applicator.

1.5 Significance of Study

This study will benefit the treatment of cervical cancer as it helps to understand the dose distribution behaviour associated with the standard tandem plus ring applicator in term of target conformity, healthy organs sparring and finally to distinguish the difference between the dose calculated by the treatment planning system (TPS) and the measured dose by using the dosimeter system. This is important to verify the reliability of the treatment planning system with the algorithm used so that the dose can be delivered as planned and treatment effectiveness can be achieved when it is applied to cervical cancer patients in clinical setup.

CHAPTER 2

LITERATURE REVIEW

2.1 Cervical cancer

Cervix is a female reproductive system that connected the body of the uterus to the vaginal canal located at the pelvic region of the body. It is guarded by two orifices. As in Figure 2.1, the external orifice (ectocervix) opens into the vagina, and the internal orifice (endocervix) leads to the uterus. The structures typically made by epithelial lining with variety of cells such as squamous and glandular cells. Cervical cancer develops from aberrant cell proliferation, which is mostly caused by infection with specific strains of human papillomavirus (HPV). Persistent infection of HPV can gradually progress the changes into cervical cancer over time (Sahoo, Satyanarayana & Nayak, 2014).

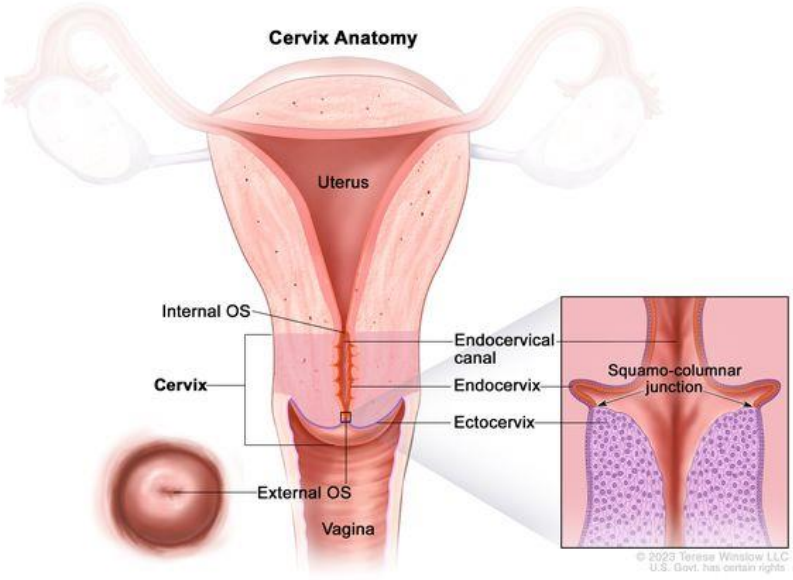

Figure 2.1 shows the illustration of cervix structures. (Cancer.gov, 2024)

Zhang *et al.* (2021) reported in their survey that the worldwide trend of incidence, mortality, and disability due to cervical cancer was observed reducing at a moderate rate between 1990 to 2019. The trends were quite gradual, and there was significant geographical disparity. However, the incidence is alarmingly high in some regions of the world, this includes sub-Saharan Africa, Latin American nations, India, and South-East Asia.

This is consistent with research conducted by Zhao *et al.* (2022) which found that cervical cancer is a serious health concern in ASEAN nations. In 2020, it ranked among the top five cancers affecting women in all ASEAN countries except Vietnam and Singapore. Projections suggest ASEAN could see 99,000 new cases and 63,000 deaths from cervical cancer by 2040, marking a 44.4% and 63.5% increase from 2020, respectively. Malaysia specifically anticipates an over 80% rise in cervical cancer fatalities by 2040.

Until recently, the International Federation of Gynaecology and Obstetrics (FIGO) criteria were referred to determine the staging of cervical cancer. In 2018, the Gynaecologic Oncology Committee updated FIGO staging to include imaging and pathology data. (Bhatla *et al.*, 2018). Typically, most cancers have stages I until IV. However, for cervical cancer the stages ranging from 0 to IV. The staging has been listed by Bhatla *et al.* (2018) as in Table 2.1.

Table 2.1 shows the 2018 FIGO staging of cervical cancer.

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumour size and extent (with r and p notations)
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous edema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

The treatment for cervical cancer varies by stage of malignancy and involves multiple medical specialties. For Stage 0, common treatments include cryosurgery, laser surgery, and loop electrosurgical excision procedure (LEEP). Stage I options include various types of hysterectomy and lymphadenectomy. Stage II treatments involve more extensive surgeries like radical hysterectomy and pelvic node dissection. Stage III is typically managed with radiation and concurrent chemotherapy, while Stage IV often requires a combination of chemotherapy, radiation, and palliative care. However, treatment methods can differ between medical institutions, and additional adjuvant treatments may be used to prevent recurrence (Bhatla *et al.*, 2018, Cohen *et al.*, 2019 and Johnson *et al.*, 2019).

2.2 Brachytherapy

Radiation therapy for cancer treatment can be divided into several subfields such as external beam radiotherapy (EBRT), internal radiation therapy (brachytherapy – BT), intraoperative radiation therapy, systemic radiation therapy, and radioimmunotherapy. However, popular radiation therapy approach for cervical cancer treatment is the EBRT and BT which typically done concurrently to obtain better treatment outcome. EBRT involves the delivery of radiation from a linear accelerator to the treatment area externally meanwhile BT is described as a booster to treatment the area. Brachytherapy is defined as a short-distance radiation treatment on the cancer tissue that employs the use of radioactive sources with different dose rates and being placed in close proximity to the treatment region (Delvin *et al*., 2016).

According to Suntharalingam, Podgorsak & Tolli (2006), the major benefit of brachytherapy techniques in cancer treatment is the great accuracy and precision of delivered doses to target volume while sparring of normal tissues. Compared to EBRT, brachytherapy has the ability to deliver a high dose of radiation to a localised tumour in a conformal fashion with simultaneous sparing of organs at risk (OARs) due to a rapid dose fall off. Meanwhile, the EBRT will give unnecessary radiation dose to organ surrounding the target volume as a result of dose build up and exit dose.

Based on a review made by Banerjee & Kamrava (2014), brachytherapy can be classified according to several aspects. Firstly, the classification based on the source implants. Recently, BT implantation techniques are divided into five categories which is intracavitary (source placement into body cavity), interstitial (source direct implantation into tumour volume), surface mould which the source loaded into plaque/mould which is brought into contact with the skin surface), intraluminal (source

insertion into hollow organs or lumen, and lastly, intravascular where the source is brought to the targeted area intravenously.

Next classification of BT with respect to the treatment duration. It is divided into two types which is temporary and permanent. Temporary implant described as dose delivered over a short period of time in comparison with source's half-life. The source is removed when the prescribed dose has been reached. Meanwhile, the permanent implant described as dose delivered over the lifetime of the source until it undergoes complete radioactive decay. This approach also known as seed implantation technique. Another classification of brachytherapy is according to the dose rate of the radioactive source. This includes high dose rate (HDR) brachytherapy, low dose rate (LDR) brachytherapy, medium dose rate (MDR) brachytherapy, and pulsed-dose rate (PDR) brachytherapy.

However, HDR brachytherapy is the most common approach that being practiced at many medical institutions nowadays. Brachytherapy also can be classified with respect to the source loading pattern. It is classified into two categories which is hot loading that involve applicator placement with pre-loaded radioactive source at the time of insertion into patient. Secondly, the after loading approach where it involves the placement of empty applicator first inside patient and follows later insertion of radioactive source. This approach has also been divided into two categories which is manual afterloading (source placement by hand-held tools) and remote afterloading (motor driven transport system).

With remote afterloading technology, it enables a small radioactive source attached to the end of a cable to be automatically driven across numerous channels. This enable the source to be located as specific point (dwell point) for specific duration

(dwell time). The dose rate for HDR BT source typically greater than 12 Gy/hour and nowadays majority institutions are using the iridium-192 isotope. HDR BT has several advantages, including accurate source positioning, infinitely variable dwell lengths and dwell positions (allowing for dose sculpting), quicker treatment times, and radiation protection for health care personnel. HDR BT treatment has quickly grown, and overall survival is comparable with LDR BT (Sonali *et al.*, 2015).

Data from several publications demonstrate variations in the percentage of overall survival rate and treatment result for cervical cancer utilising brachytherapy. Tharavichitkul *et al.* (2022) evaluated cervical cancer patients treated with image-guided brachytherapy (IGBT) and found that the four-year local control, progression-free survival, and overall survival rates were 89.5%, 74.9%, and 69.1%, respectively. Meanwhile, Alfrink *et al.* (2024) did a clinical study of the quality of life for cervical cancer patients who had radio chemotherapy (RCT) and brachytherapy (BT) as the ultimate treatment.

The five-year overall survival (OS), distant metastasis-free survival, and pelvic tumour-free survival rates were 53%, 54%, and 83%, respectively. Furthermore, Yu *et al.* (2023) evaluated the function of brachytherapy for post-operative cervical cancer patients, finding that brachytherapy provided a greater advantage in avoiding local recurrence with an 87.7% mean and an overall survival rate up to 78.4%. This demonstrates that brachytherapy is one of superior approaches with more than 50% of positive outcomes in treating cervical cancer worldwide.

However, to achieve this positive treatment outcomes in brachytherapy, it involves intricate workflow. An article from Chargari *et al.* (2019) simplify the general brachytherapy workflow in clinical settings. First step involves the diagnosis done by

oncologist to determine suitable type of BT technique to be used. Secondly, the selection of applicator implantation procedure that depends on the tumour topography, size, and OARs proximity. Next, the image acquisition procedure that involve the use of imaging modalities such as general X-ray, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). This to enable the visualisation of the implants relative to the patient anatomy, this step also helps for target definition, dose calculation and treatment simulation.

The 2D or 3D based images are used in the treatment planning process to calculate the optimum dose to be administered to treatment area. This phase is one of critical steps in brachytherapy treatment delivery chain because it determines the dose distribution produced by the point source using specific formalism. During treatment planning, the tumour dose objectives and OARs dose constraints need to be analysed accurately. Moreover, to evaluate the dose calculated in the treatment planning system, pre-treatment quality assurance and quality control tests need to be done. This to ensure the dose delivered to be patient reflects the planned dose in TPS. Meanwhile, the quality control (QC) tests are required to prevent any malfunctions related to the instrumentation and equipment used during treatment delivery.

2.3 TG-43 formalism

The most vital part in brachytherapy chain is the calculation of the dose distribution produce by radioactive source that will to be administered to the patient. Nowadays, calculations are performed using formalism set by the American Association of Physicists in Medicine (AAPM). They constituted a Task Group No. 43 to review the current publications on dosimetry of interstitial BT sources and suggest a dosimetry

procedure that would contain a formalism for dose calculation including the necessary dosimetry parameters.

The formalism illustrates the dose calculation with the parameters for commonly used BT sources like iridum-192 in two dimensions (Figure 2.2). Since the real clinical environment utilises a BT source within the body, with water accounting for 70% of the human tissue composition, the report discusses the prior issue by utilising a measured dose distribution produced by a source in a water equivalent medium (Rivard *et al.*, 2004 and Rivard *et al.*, 2009).

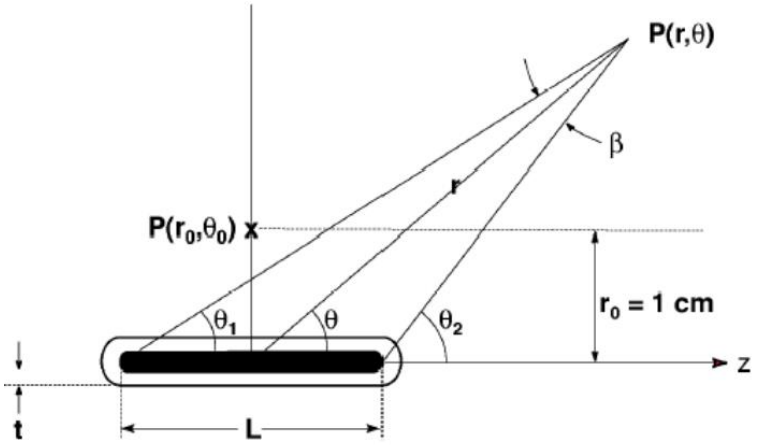

Figure 2.2 shows the geometry used in the calculation of dose distribution near a linear source. (Rivard et al., 2009).

According AAPM TG-43 report, the dose distribution can be calculated using a polar coordinate system with origin is located at the center of the source. Dose rate $D(r,\theta)$ produced by the source at the point of interest $P(r,\theta)$ in water is expressed by:

$$D(r,\theta) = S_k \Lambda \frac{G(r,\theta)}{G(r_0,\theta_0)} g(r) F(r,\theta)$$

where, r is defined as the distance of point P from the origin (cm), θ is the angle between the direction of radius vector, r to the long axis of the source, S_k described as the air kerma strength of the source. ($\mu Gy.m^2.h^{-1}$), Λ is referred as the dose rate constant in

water, $G(r,\theta)$ is the geometry function, $g(r)$ is the radial dose function, and lastly, $F(r,\theta)$ referred as the anisotropy function.

Air kerma strength and dose rate constant is both affected by the type of radionuclide and the design of the source, particularly its core and encapsulation. The geometry function accounts on how the form of the source influences the dose. Meanwhile, the radial dose function describes the decrease in dose rate along the transverse axis caused by medium absorption and scattering. This function is also impacted by photon filtering caused by the source's encapsulation and material. Finally, the anisotropy function depicts the dose distribution around the source, taking into account the effects of absorption and scatter in the medium (Saw, Meigooni & Nath, 1998).

Even though the formalism is the key role for calculating dose in brachytherapy, there are several limitations possess by this method with its implementation inside treatment planning system. The fact it used the calculation inside homogenous water medium make the TPS to ignore the tissue heterogeneity in real clinical cases (Lee, 2014). Previously, Rivard, Venselaar & Beaulieu, (2009) have listed several limitations possess by the formalism, which include the differences between dose in water and human tissue, differences between attenuation of radiation in water and tissue, the presence of source shielding, the interactions between applicator materials and differences between scattered radiation for data acquisition and patient related input data.

Furthermore, despite the emergence of modern imaging based TPS and dose delivery systems, the data provided from patient imaging has not been fully used. It disregards the patient-specific radiation interactions as well as radiobiological

variations between different tissue compositions causing the inability to accurately handle interactions within the patient such as scatter radiation (Peppa *et al.*, 2016).

In addition, Lee (2014) also discussed the clinical circumstances that highlight the limitations of the formalism particularly in various anatomic sites such as prostate, breast, gynaecologic, lung, and eye causing the discrepancies between planned and delivered dose to occur. This demonstrates that the AAPM TG-43 dosimetry formalism fails to account for key critical factors that undermine clinical applicability.

2.4 Gynaecological Brachytherapy Applicators

Based on the brachytherapy implantation approach, the most common method for treating cervical cancer is intracavitary brachytherapy. It involves insertion of a radioactive source into the vaginal cavity via an applicator to deliver radiation dose to the upper vagina, cervix, and uterus. Meanwhile, interstitial brachytherapy involves placing catheters (small tubes) in and around residual tumour using a trans-perineal/vaginal technique (Delvin *et al*., 2016). There is a various type of applicator that is available for intracavitary brachytherapy.

Tandem and Ovoid (TO) and Tandem and Ring (TR) are the most frequently employed applicators where the TO comprises of an intrauterine tube (tandem) that placed through the cervix to the level of the uterine fundus, and two ovoids placed on sides of the cervix in the lateral vaginal fornixes. The TR is likewise a tandem, with a ring placed on either side of the cervix. These two applicators differ in terms of simplicity of use and radiation dose distribution. However, both have comparable results (Banerjee and Kamrava, 2014).

In particular, a recent article outlines how the conventional tandem plus ring applicator was designed as a derivative of the Stockholm tandem-and-box approach.

Originally, metallic ring applicators of varying diameters were used. Nowadays, the intrauterine tube of the applicator comes in a variety of materials, lengths (e.g. 20, 40, 60 mm) and angles (e.g. 30°, 45°, 60°). The ring placed perpendicular to the tandem and had known geometry since the tandem is fixed in the ring's centre. The ring applicator works best for individuals who have shallow lateral fornixes (Mourya, Aggarwal & Choudhary, 2021).

Recently, the adoption of image-guided brachytherapy (IGBT) has increased the popularity of CT/MR compatible applicators. It involves the image acquisition using computed tomography (CT) or magnetic resonance imaging (MRI). Metallic applicators are proven to cause streak artefacts on CT images. This makes the image quality deteriorates due to beam hardening and photon starvation. As a result, applicator reconstruction and structures contouring on deteriorated images influence the plan quality and the calculated dose distribution (Wu *et al.*, 2015).

To overcome the issue, various research proposed new materials for the CT/MR applicator. This includes the consideration on the usage of low atomic (Z) number materials such as PPSU or Epoxy Polyvinyl Ester Polyester Glass Fibre. The overall goal of CT/MR applicators is to employ robust composite fibre tubing and plastic to prevent distortion of the CT or MR images (Mourya, Aggarwal & Choudhary, 2021).

2.5 Dosimetric Analysis on the usage of Gynaecological Applicators.

According to Suntharalingam, Podgorsak & Tolli (2006), one of the aspects that affected any brachytherapy treatment outcome is the particular model used for the source distribution at the target volume. This includes the geometry of the equipment used during the treatment delivery such as the applicators itself. Hence, dosimetry analysis related to the usage of the applicators is important aspect in the brachytherapy

treatment delivery. Most the dosimetric evaluation in cervical brachytherapy often comparing between types of applicators.

For example, dosimetric analysis done by several researchers from 2008 to 2020. The studies analysed between common applicator types that employed in cervical cancer brachytherapy which are tandem and ring (TR) and tandem and ovoid (TO). Similarly, the evaluation was done on the dose distribution inside TPS with the aim to deliver the prescribed dose at specific points while maintaining a traditional pear-shaped dose distribution. Result for research in 2008 by Levin *et al.* found no significant differences in doses to critical areas between TR and TO applicators.

However, TO applicators are found to treat larger volumes for longer durations, potentially over-treating healthy tissue, while TR applicators might not deliver enough dose to tumour tissue. The results are consistent with the research in 2015 done by Ma *et al.,* where the TR applicator treated a smaller total tissue volume without compromising the dose distribution to the tumour volume. Rangarajan (2018) made some additional evaluation on the dosimetry analysis by using larger sample sizes for their study. They analysed more point doses on OARs, and treatment time associated with these types of applicators.

The results also consistent with previous findings, which found that TO applicators resulted in greater bladder and rectal doses and bigger treatment volumes. Despite the large treatment volume, tumour coverage and short-term toxicity were identical with TR applicator. Tandem-ovoid applicators also recorded to has a slightly greater dose at point-B, meanwhile, the mean D_{2cc} dose for the bladder and rectum was lower with tandem-ring applicators. Minor dosimetry discrepancies were noted between

these two applicators, with the decision commonly determined by the patient's anatomy, TR applicator was preferred for individuals with limited space for two ovoids.

Recent research done by Biltekin *et al.* (2020) found no significant differences in D_{90} values of HRCTV between the two applicators. However, TR with rectal retractor was significantly better than TO in terms of rectal dose. Additionally, there were no statistically significant differences in D_{2cc} values foremost OARs. However, the mean D_{2cc} value for all defined OARs was lesser in TR compared with TO applicator.

A different study made by Abdullah *et al.* (2015) and Dumane *et al.* in 2017 which they assess the different influence of different applicators geometry in treating cervical cancer. Abdullah *et al.* (2015) did a retrospective study to assess the OARs doses estimated based on ICRU reference point calculated in two-dimensional (2D) radiographs. The treatment plans were created based on patients who received brachytherapy treatment using different length and size of gynaecological applicators. They found that the combination of ovoid size, tandem length, and anatomical changes across patients were contributing factors that influences the dose to OARs. It was observable that the OARs dose varied among different applicator configurations used for ICBT.

Meanwhile, Dumane *et al.* in 2017 utilised the same type of applicator which is tandem and ring applicator but with changes in applicator angles, ring diameter, and tandem lengths. The study found that the changes of angulation and ring diameter also change the dose distribution because it gives different doses to the OARs in the DVH analysis. This shows that selecting the correct angle of applicator and ring diameter for the subsequent fractions can assist reducing OARs dose, while also help to achieve the dose constraints.

It is concluded the gynaecological applicators have similar characteristics in term of the aim of use. However, the dose distribution produced by these types of applicators have some differences. Most of previous studies did dosimetry analysis by evaluating parameters such as the target coverage which dose to 90% (D_{90}) or 95% (D_{95}) of the target volume (HRCTV - High-Risk Clinical Target Volume). Meanwhile the evaluation on the organ at risks (OARs) involves the dose received by the bladder, rectum and sigmoid as those organs located near to the treatment area. This to ensure that dose constraints are met to minimise toxicity.

2.6 Dose verification in Brachytherapy

The dose verification in brachytherapy is a pre-treatment quality assurance step prior to the treatment delivery. This step is vital to ensure the dose delivered to the target volume and adjacent healthy organs reflects the dose calculated in the treatment plan. It involves analysis of the discrepancies between the dose calculated by the treatment planning system and the actual dose measured using dosimeters (Mayles, 2013). In addition, in vivo dosimetry is also a method for detecting systematic mistakes and preventing unintentional radiation doses during treatment delivery.

Although it will not prevent the misadministration of a single dose, it will reduce the chance of such an occurrence spreading to several treatments. Early in the course of treatment, in vivo dosimetry can detect radiation under- or overdose, allowing modifications to be made in later irradiation sessions (Kertzscher *et al.*, 2014). Existing studies show variations in the dose verification methods, including the implementation of different type of dosimeters, production of phantoms for experimental setup and real time verification inside patient.

Gambarini *et al.* (2012) conducted a real-time in vivo verification, evaluating the possibility to perform in vivo rectal dosimetry. It was done by placing thermoluminescence detectors (TLDs) at transrectal ultrasound probe adopted during brachytherapy boosts of prostate cancer patients. The finding reveals an excellent agreement between the intended dose and TLDs dose measurements with only one TLD obtained dose value higher than 10% for one patient. Even though the study makes it possible to measure dose within patient during BT treatment delivery, this only limited to specific location such as rectal and prostate area.

Palmer, Bradley & Nisbet (2012) and Jayakody *et al.* (2022) reviewed articles on dose accuracy in HDR brachytherapy related to dosimetry and verification techniques. The aim was to evaluate practical methods for dosimetry, dose rate field determination, treatment planning system capabilities, treatment unit performance, and dose delivery verification. The studies mentioned that in vivo verification of treatment plan accuracy is desirable, but many uncertainties involved. Thus, an alternative or additional approach prior verification is required by using experimental setup in phantom measurement. The experimental setups show that the deviation between measured and calculated doses is up to 11.5%.

On the other hand, a study done by Oshaghi *et al.* (2013) to compare the dose between Monte Carlo simulation, treatment planning (FlexiPlan software), and TLDs measurement. The study was done using specialised applicator for breast brachytherapy and the measurement was done using female chest phantom. The result shows acceptable agreement (less than 8%) between the results. But the study also found several vital criteria to achieve successful treatment planning and dose delivery. These criteria include the accurate source locations, accurate definition of target and OARs, and careful determination of uncertainties.

Meanwhile, study made Nikoofar *et al.* (2015) and Moura *et al.* (2018) highlight the usage of heterogenous phantom for dose verification in brachytherapy. Nikoofar *et al.* (2015) made a study on oesophageal cancer brachytherapy and an anthropomorphic phantom was developed. The phantom comprised natural bone and a paraffin wax-sodium chloride mixture mimicking soft tissue. TLD measurements were done on OARs like eyes and glands, and it showed higher doses than TPS calculations. The discrepancies were concluded majorly due to heterogeneity of tissue overlooked in TPS and distant regions received scattered radiation, while closer ones received primary radiation, affecting dose distribution.

In study made by Moura *et al.* (2018), the phantom was created using water, cork, and aluminium to test HDR brachytherapy treatment planning system (TPS) algorithms. TLDs were used to measure TL responses and compared with Gafchromic EBT3 film, MC code, and TPS. Five TLDs were positioned at the center of phantom for each setup, and measurements were normalised to values from a homogeneous setup. The dose distribution in the phantom aligned well with simulations and TPS calculations, though differences in dose responses were observed due to heterogeneity. Thus, both studies emphasised the need to consider heterogeneous effects in HDR brachytherapy.

Furthermore, Gadhi *et al.* (2016) conducted a phantom experiment to assess diode dosimetry and verify dose accuracy for various in vivo dosimetry HDR BT applicators, including those for oesophagus, rectum/vagina, and cervix (Fletcher & Ring). Using a 3D water phantom to simulate clinical conditions, dose measurements were compared with TPS calculations using radiographs of all components. Results showed a small average percentage difference between TPS and diode doses across all

measurements (1.87% ± 2.64), indicating good agreement (~2%) for different clinical scenarios.

This in-vivo phantom dosimetry study provides confidence in prescribed treatment delivery and enhances HDR brachytherapy treatment reliability. At the same year, Gholami *et al.* verified dose distributions calculated by the TG-43 formalism for gynaecological brachytherapy using EBT Gafchromic film. They employed a solid water phantom designed to fit a tandem and ovoid assembly for HDR and LDR brachytherapy. They found the deviations between expected and measured data ranged from 2.4% to 3.8% respectively.

Zwierzchowski, Bieleda & Skowronek (2017) created a similar study to verify a new calculation algorithm. The study utilised gamma analysis to evaluate the dose distribution and the result shows good agreement between the evaluated parameters. It was mentioned that film dosimetry system seems to be offered a quick and dependable method for calculation algorithm commissioning, treatment planning validation and treatment delivery. However, the dosimetric information measured by film only give 2D or planar dose distribution and there is no information about the dose received by adjacent tissues.

A recent study sought to develop a dosimetry verification system for HDR BT that would use a solid water phantom for patient-specific quality assurance (PSQA). The study advocated three steps which is dose measurement, calculation, and analysis. Dose distribution was measured with EBT3 film within a simple solid water phantom, and gamma analysis with a 3% dose difference and 3 mm distance-to-agreement criterion was employed. Results highlight careful measurement and correct determination of the correction factor, the system was highly effective for patient-

specific QA in HDR brachytherapy (Kang et al., 2021). However, the study only evaluated dose distribution in a simple setup without using complex applicators.

Lastly, Moonkum *et al.* (2023) conducted a study similar to previous research, aiming to do dose verification using a diode rectal dosimeter in a in house pelvic phantom. They found that the percentage differences between the diode and the TPS ranged from -3.3% to 4.1%. Statistical analysis revealed no significant discrepancy between the doses from the detector and the treatment planning system, and the comparison indicated that the percentage difference was acceptable for in-vivo dosimetry in brachytherapy. The study also recommended the diode dosimetry could be an excellent dosimeter for a treatment verification method in cervical cancer brachytherapy.

In summary, dose verification procedure in brachytherapy can be done for real time measurement in patient, experimental using phantoms, and computational using simulation software. The experimental methods highly depend on the design of the phantom, phantom material, and dosimeters' type. Meanwhile, the computational method depends on different type of Monte Carlo codes to simulate the dose calculation (Jayakody *et al.*, 2022). The studies also provide a general guideline to create an in vivo dosimetry procedure for brachytherapy. It involves the suitable selection of the dosimeter, suitable dosimeter calibration method, usage of homogenous or heterogenous phantom, careful determination of dosimeter locations inside phantom, phantom irradiation and lastly establishment of the data analysis procedures.

2.7 Thermoluminescent Dosimeter (TLD) usage in Brachytherapy Dosimetry.

Radiation dosimeter typically is a device, equipment or system that measures or analyses the quantities that related to ionising radiation such as absorbed dose. Meanwhile, a dosimetry system is referred as combination of the dosimeters and their respective reading system. Generally, the ideal dosimeter properties used in brachytherapy can be characterised by accuracy, linearity, dose-rate dependence, energy response, angular dependence, and spatial resolution (Izewska & Rajan, 2005).

Many studies suggest employing different types of dosimeters to evaluate dose distribution around the brachytherapy source. Dosimeters include ionisation chambers, solid sates, detectors, radiochromic films, thermoluminescent dosimeters, scintillation detectors, and gel dosimeters. However, Jayakody *et al.* (2022) reported that thermoluminescent dosimeters (TLDs) are often utilised for dose estimation in brachytherapy dosimetry. TLDs are useful in clinical settings since they are physically tiny compared to other dosimeters. It comes in many forms such as powder, chips, rods, and threadlike.

According to Le Guillou *et al.* (2017), the basic principle of TLDs in measuring radiation dose is the energy received by TLDs from radiation and cause small proportion of electron to be excited to the conduction band and travel until it trapped in the forbidden zone, the electron will remain until it is being released by subsequent heating. During heating process, the electrons get enough energy to rise to the conduction band, from where they can return to their bound energy levels by emitting visible light.

By integrating the amount of light emitted during heating process, the energy deposited during irradiation or known as absorbed dose can be obtained. The detectors rely on the fact that electrons in some materials can be trapped in metastable states when