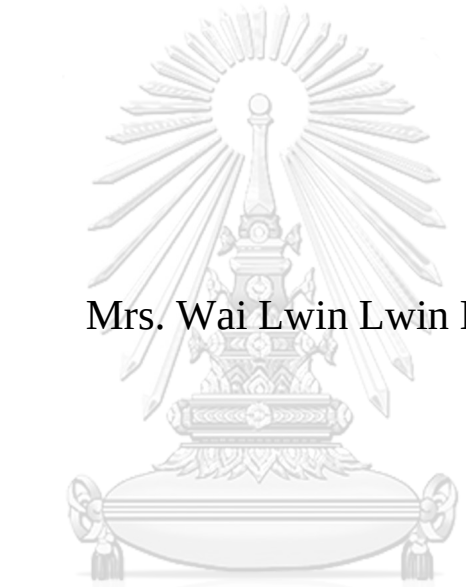
Dosimetric comparison between single and double isocenters Volumetric Arc Therapy for Stereotactic Radiotherapy with multiple targets

Mrs. Wai Lwin Lwin Kyaw



A Thesis Submitted in Partial Fulfillment of the Requirements
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การเปรียบเทียบปริมาณรังสีระหว่างการใช้จุดหมุนหนึ่งและสองจุดในการฉายรังสีศัลยกรรมที่มีก้อนมะเร็งหลายก้อนด้วยเทคนิค VMAT

นางไว ลวิน ลวิน จอว์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาฟิสิกส์การแพทย์ ภาควิชารังสีวิทยา
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Thesis Title	Dosimetric comparison between single and double isocenters Volumetric Arc Therapy for Stereotactic Radiotherapy with multiple targets
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Field of Study	Medical Physics
Thesis Advisor	TAWEAP SANGHANGTHUM, Ph.D.

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ไว ลวิน ลวิน จอว์ : การเปรียบเทียบปริมาณรังสีระหว่างการใช้จุดหมุนหนึ่งและสองจุดในการฉายรังสีศัลยกรรมที่มีก้อนมะเร็งหลายก้อนด้วยเทคนิค VMAT. (Dosimetric comparison between single and double isocenters Volumetric Arc Therapy for Stereotactic Radiotherapy with multiple targets) อ.ที่ปรึกษาหลัก : ทวีป แสงแห่งธรรม

วัตถุประสงค์ของงานวิจัยนี้เพื่อประเมินผลทางรังสีระหว่างการใช้ 1 และ 2 จุดหมุน ในการรักษาวิธีรังสีร่วมพิกัดบริเวณสมองด้วยเทคนิคการฉายรังสีปรับความเข้มโดยหัวเครื่องหมุนรอบตัวผู้ป่วย แบ่งงานวิจัยเป็น 2 ส่วนได้แก่ส่วนการทดลองเพื่อเลือกพลังงานที่เหมาะสม และประยุกต์ใช้ทางคลินิกเพื่อใช้เทคนิคที่เหมาะสม ทำการวางแผนการรักษาโดยใช้พลังงาน 6 MV, 10 MV, 6 FFF และ 10 FFF บนภาพเอกซเรย์คอมพิวเตอร์ที่จำลองรอยโรค 3 ก้อน และระยะ 3 ซ.ม.ระหว่างก้อน จากนั้นเมื่อได้พลังงานที่เหมาะสม ทำการปรับเปลี่ยนขนาด, จำนวน และระยะห่างระหว่างก้อน ทั้งสิ้น 18 รูปแบบ บนภาพเอกซเรย์คอมพิวเตอร์ โดยใช้เครื่องวางแผนการรักษาอีคลิปส์ เวอร์ชัน 15.0 แผนการรักษาประกอบด้วย 3 เทคนิค ได้แก่ หมุนเครื่อง 2 รอบบนระนาบเดียวกันโดยใช้ 1 จุดหมุน (2 Arcs SI), หมุนเครื่อง 1 รอบบนระนาบเดียวกัน และหมุนอีก 2 ระนาบโดยใช้ 1 จุดหมุน (3 Arcs SI), หมุนเครื่อง 1 รอบบนระนาบเดียวกัน และหมุนอีก 2 ระนาบต่อจุดหมุนโดยใช้ 2 จุดหมุน (6 Arcs DI) กำหนดปริมาณรังสีที่ 21 เกรย์ที่ทุกก้อนรอยโรคใน 3 ครั้ง ประเมินแผนการรักษาโดยใช้ ดัชนีความเข้ารูป (CI_{RTOG}), ดัชนีความสม่ำเสมอ (HI_{RTOG}), และดัชนีความลาดชัน ($GI_{Paddick}$) สำหรับก้อนมะเร็ง และใช้ปริมาตรที่ได้รับรังสี 6 และ 12 เกรย์สำหรับประเมินผลที่สมอง ทำการกำหนดค่าปริมาณรังสีระหว่างการคำนวณของแต่ละอวัยวะให้เท่ากันทั้ง 3 เทคนิคการรักษา ผลการรักษาพบว่า การใช้พลังงาน 6 FFF เป็นทางเลือกที่เหมาะสมที่สุด เนื่องจากให้ค่าดัชนีความเข้ารูปและความลาดชันที่ดีที่สุดเมื่อเปรียบเทียบกับพลังงาน 6 MV, 10 MV และ 10 FFF จากนั้นเมื่อปรับเปลี่ยนขนาด, จำนวน และระยะห่างระหว่างก้อนโดยใช้พลังงาน 6 FFF พบว่าค่าดัชนีความเข้ารูปเฉลี่ยของการใช้ 3 รอบการหมุนจาก 1 และ 2 จุดหมุน อยู่ที่ 14.79 ± 5.83 และ 13.70 ± 4.72 ตามลำดับ ซึ่งดีกว่าการใช้ 2 รอบการหมุน (17.56 ± 6.15) ขณะที่ค่าดัชนีความเข้ารูปและความสม่ำเสมอใน 3 เทคนิคไม่มีความแตกต่างกัน นอกจากนี้ดัชนีความเข้ารูปและความลาดชันระหว่าง 3 รอบการหมุนด้วย 1 และ 2 จุดหมุนไม่มีความแตกต่างกันอย่างมีนัยสำคัญ แต่แผนการรักษาแบบ 2 จุดหมุนให้ค่าความสม่ำเสมอของปริมาณรังสีที่ดีกว่าอย่างมีนัยสำคัญทางสถิติ ในส่วนของปริมาตรสมองที่ได้รับรังสี 12 เกรย์ ทั้ง 3 เทคนิคให้ผลไม่แตกต่างกัน แต่ในปริมาตรสมองที่ได้รับรังสี 6 เกรย์ พบว่า การใช้ 3 รอบการหมุนโดย 1 และ 2 จุดหมุน อยู่ที่ 77.40 ± 34.30 ซม^3 และ 68.94 ± 30.50 ซม^3 ตามลำดับ ซึ่งน้อยกว่าการใช้แบบ 2 รอบการหมุนใน 1 จุดหมุน (108.10 ± 57.20 ซม^3) อย่างไรก็ตาม การใช้ 2 จุดหมุนเป็นการเพิ่มเวลาในการฉายรังสีประมาณ 2 เท่า ดังนั้นจึงสามารถสรุปได้ว่า การใช้ 3 รอบการหมุนจาก 1 จุดหมุน เหมาะสมที่สุดสำหรับการวางแผนการรักษาวิธีรังสีร่วมพิกัดบริเวณสมองด้วยเทคนิคการฉายรังสีปรับความเข้มโดยหัวเครื่องหมุนรอบตัวผู้ป่วย ที่มีรอยโรคขนาด 2-5 ก้อน

สาขาวิชา	ฟิสิกส์การแพทย์	ลายมือชื่อนิสิต .....
ปีการศึกษา	2562	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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Wai Lwin Lwin Kyaw : Dosimetric comparison between single and double isocenters Volumetric Arc Therapy for Stereotactic Radiotherapy with multiple targets. Advisor: TAWEAP SANGHANGTHUM, Ph.D.

The purpose of this study was to evaluate the dosimetric effects between single isocenter (SI) and double isocenters (DI) VMAT SRT of multiple brain metastases. There are two parts of study, which were experimental for energy selection, technique comparison and clinical part to use appropriate technique. As the first part, three lesions with 3 cm distance apart and 1 cm size for all lesions were created as standard plan by varying energy. Twelve VMAT SRT plans by varying energy with 6 MV, 10 MV, 6 FFF and 10 FFF were planned on simulated three lesions of CT image. 18 VMAT SRT plans with varying lesions size, number and distance were simulated on patient CT image using Eclipse treatment planning system version 15.0. The plan consisted of 3 techniques in: 2 coplanar arcs SI (2 Arcs SI), 1 coplanar combine with 2 non-coplanar arcs SI (3 Arcs SI) and 1 coplanar and 2 non-coplanar arc DI (6 Arcs DI). The VMAT plans were generated with 21 Gy prescription dose to all lesions in 3 fractions. The plans were evaluated in terms of Conformity index ($CI_{Paddick}$), Homogeneity index (HI_{ICRU}), and Gradient index ($GI_{Paddick}$) for PTV and V_{12Gy} and V_{6Gy} for normal brain. The same dose constraints were used to optimize for all cases. The results showed that 6FFF was suitable energy to apply the technique comparison because it provides the best conformity and gradient parameters when compared to 6MV, 10MV and 10FFF energy. For the technique comparison when changing the size, number and distance between the lesions using energy 6FFF, it was found that 3 arcs SI and DI were improvement in average GI (14.79±5.83, 13.70±4.72) than the 2 arcs SI (17.56±6.15) while HI and CI values were comparable for all techniques. $GI_{PADDICK}$ and $CI_{PADDICK}$ of two techniques; 3 Arcs SI and 6 Arcs DI, were not significantly showed in results with p value while HI is slightly better in 6 Arcs DI (HI_{ICRU} p value= 0.01). For normal brain, V_{12Gy} for 2 Arcs and 3 Arcs SI plans were comparable with DI and the volumes of normal brain receiving 6 Gy in 3 arcs SI and DI (77.40 ± 34.30 cm^3, 68.94 ± 30.50 cm^3) were better than 2 arcs SI (108.10 ± 57.20cm^3). Moreover, the number of arcs and treatment time were increased by nearly 2-fold and inconvenience in practice in DI. In conclusion, 3 arcs non-coplanar SI VMAT technique was present the best in dosimetric evaluation in 2-5 lesions metastases SRT.

Field of Study: Medical Physics Student's Signature .....
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Wai Lwin Lwin Kyaw

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LIST OF ABBREVIATION

Abbreviations	Terms
2D	two dimension
3DCRT	Three-dimensional conformal radiation therapy
AAA	Analytical anisotropic algorithm
AAPM, TG	American Association of Physicists in Medicine, Task Group
BEV	Beam's eye view
BM	Brain metastasis
cm:	Centimeter
cm^3	Cubic centimeter
CT	Computed tomography
$D_{2\%}$	Maximum dose to 2% of the target volume
$D_{50\%}$	Median dose to 50% of target volume
$D_{95\%}$	Dose to 95% of target volume
$D_{98\%}$	Minimum dose to 98% of the target volume
DI	Double isocenter
DICOM	Digital Imaging and Communications
DTA	Distance to agreement
DD	Dose different
DVHs	Dose volume histogram
EBRT	External beam radiation therapy
eV	Electronvolt
FFF	Flattening filter free
GI	Gradient index
GK	Gamma knife
GTV	Gross tumor volume
Gy	Gray

HDR	High dose rate
HFSRT	Hypofractionated stereotactic radiotherapy
HI	Homogeneity index
HU	Hounsfield units
ICRU	International Commission on Radiation Units and Measurements
IGRT	Image guided radiation therapy
IMRT	Intensity modulated radiation therapy
Linac	Linear accelerator
min	Minute
MLC	Multi-leaf collimator
MRI	Magnetic resonance imaging
mA	Milliampere
MeV	Megaelectron-volts
MU	Monitoring unit
MV	Megavolts
No.	Number
OARs	Organ at Risk
PTV	Planning target volume
$PV_{50\%}$	50% of prescribe isodose volume
PV	Prescribe isodose volume
QA	Quality assurance
RT	Radiation therapy
RTOG	Radiation therapy oncology group
SD	Standard deviation
SI	Single isocenter
SNC	Sun Nuclear Corporation
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy

TPS	Treatment planning system
TV	Target volume
TV_{PV}	Target volume within the prescribed isodose surface
V_{6Gy}	Volume receiving dose of 6 Gy
V_{12Gy}	Volume receiving dose of 12 Gy
VMAT	Volumetric modulated arc therapy
Vol.	Volume
WBRT	Whole brain radiation therapy

CHAPTER I

INTRODUCTION

1.1 Background and rationale

Brain metastasis (BM) is a cancer that has spread to the brain from another location in the body. It is the most common diagnosis in patients who are referred as complications of systemic malignant disease. Morbidity and mortality rates are high in patients who develop brain metastasis. An incidence rate of 54% has been reported for BMs in patients with adenocarcinoma of the lung[1, 2]. Due to the significant of these diseases, the use of better treatment techniques also may have contributed to a higher survival rate for brain metastases.

The focal irradiation approach for BM stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) has emerged as an important modality for multiple BMs. There are the different types of treatment to brain radiation that are led from whole brain treatment to advanced SRS VMAT. Historically, whole brain radiation therapy (WBRT) was the major role treatment for patients with brain metastases but it leads to acute and late toxicities effects to patients. Today, advances in radiation therapy have played as a role to treat BMs such as SRT, an important modality for multiple BMs and small targets[1]. SRT called knifeless surgery that can treat small tumor in head region and treat with few fractions, high dose per fraction, give very high dose to tumor especially gross tumor volume (GTV) as well as fall off dose rapidly that can spare normal tissues around the tumor. SRT needs to use specific immobilization device for patient fixation because it performs to treat very small and highly precise dose to tumor. Therefore, this treatment needs very accuracy and precise for patient setting-up and image guidance before treatment.

Volumetric modulated arc therapy (VMAT) is a novel radiation treatment techniques that can irradiated the beams during gantry rotate around the patient[3]. It can achieve highly conformal dose distributions by coplanar or non-coplanar arcs and the simultaneous variation of multi-leaf collimator (MLC) positions, dose rate, and gantry speed during treatment delivery to modulate the beam intensity [1, 3]. The efficient treatment delivery gives in very short time and gets accurate and precise treatment. VMAT has been used for linear accelerator based SRT for multiple targets to be treated simultaneously using single plan with single isocenter. VMAT SRT can plan by using co-planar arc on one plane and non-coplanar arc on oblique plane with single or multi-isocenter for brain metastases.

In addition, treatment technique and energy are also needed to consider for the effect of dosimetry outcomes of patient treatment since the characteristics of each energy type are different. SRT treatment mostly uses flattening filter free (FFF) mode of the 6FFF and 10FFF energy with highest dose rate to decrease the treatment time during irradiation. The good dose distribution of target coverage and dose for organs at risk (OARs) with FFF beams gives sparing for OARs and reduction in time of treatment due to highest dose rate for FFF more than standard energies. Traditionally,

a multi-isocenter technique, for each isocenter around the individual metastatic lesions was used with linear accelerator (linac) based SRT technique for multiple metastases treatment. Clark GM et al. compared single and multiple isocenters for multi-targets and approached by using single isocenter for multi target than multi-isocenter. The main advantage of single isocenter technique is treatment time reduction during treatment compared with multi-isocenter technique. The difference of treatment planning techniques can be evaluated by qualitative and quantitative tools. The treatment plan quality evaluations expressed in terms of gradient index (GI), conformity index (CI) and homogeneity index (HI). The quantitative evaluation includes the goal dose, minimum dose, maximum dose, and dose to normal tissues.

VMAT delivery is complicated in clinical situation because it involved various gantry speed, multi-leaf collimator speed and dose rate variation for beam modulation. VMAT patient specific QA is important to assess the coordination parameters and delivery accuracy. Arc-CHECK phantom is one of the novel equipment intended for patient specific QA. The VMAT patient specific QA measurements with ion chamber and Arc-CHECK phantom are consistent with the treatment planning system dose calculation and verification[4].

This study aimed to evaluate the dosimetric effects between single isocenter (SI) and double isocenters (DI) VMAT SRT of multiple brain metastases.

1.2 Research objective

To evaluate the dosimetric effects between SI VMAT and DI VMAT by various lesion numbers, locations, and sizes in terms of conformity index (CI), gradient index (GI) and homogeneity index (HI) for PTV and, V_{12Gy} and V_{6Gy} for normal brain sparing.

CHAPTER II

Review of Related Literatures

2.1 Theories

2.1.1 Brain carcinoma

The locations of metastasis in malignant melanoma is frequently occurred in the brain[5]. Brain cancer is usually come from brain tumor that occurs when abnormal cells inside the brain tissue. There are two main types of tumor, which are primary tumor starting within the brain, and secondary tumor spreading from elsewhere, known as brain metastasis tumors and metastatic brain tumor. The most common sites of primary cancer that metastasize to the brain are lung, breast, colon, kidney, and skin cancer. Brain metastases can occur months or even years after their primary cancer is treated. It has a poor prognosis for cure, but modern treatments are allowing to live months and years after the diagnosis[6].

Figure 2. 1 Patient with brain multiple metastases

Nowadays, BMs are the most common diagnosis in patients who are referred as complications of systemic malignant disease as shown in Figure 2. 1. Morbidity and mortality rates are high in patients who develop brain metastasis. An incidence rate of 54% has been reported for brain metastases in patients with adenocarcinoma of the lung[2, 7]. Due to the significant of these diseases, the use of better treatment techniques also may have contributed to a higher survival rate for brain metastases. There are the different types of treatment to brain radiation that are led from whole brain treatment to advanced SRS as shown in Figure 2. 2.

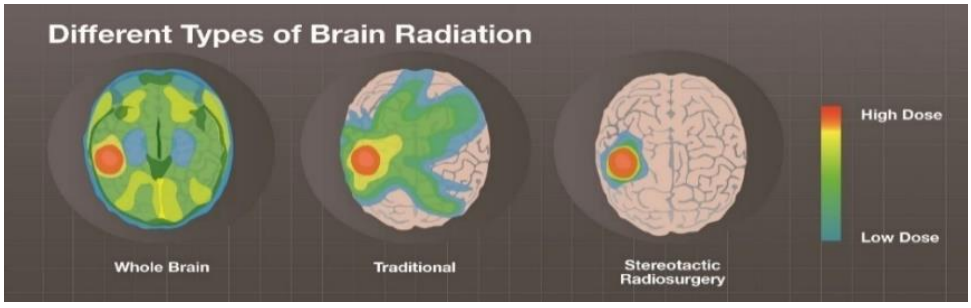


Figure 2. 2 Different types of treatment for brain metastases

Whole brain radiation therapy (WBRT) was used for patient with brain metastases in most previous treatment, but more normal brain tissue was irradiated with WBRT resulting in more side effects such as acute and late toxicities for patient. Todays, the SRS/SRT techniques are advanced to the treatment of multiple brain metastases with single fraction SRS or hypofraction of SRT in oncology.

2.1.2 The incident of brain metastases

Brain metastases significantly impact with systemic malignancy during patients by clinically. One of the studies evaluated that they diagnosed seventy-one percent of patients with additional extracranial metastases and in 46%, more than one organ system was affected, including lung in 54%, liver in 35%, bone in 16% and skin in 42%. Sixteen percent of patients had distant lymph node metastases[5].

2.1.3 Patient Immobilization

The specific immobilization device is the important section of SRT treatment. It needs to use for patient fixation as shown in Figure 2. 3 because SRT treatment delivered with highly precise dose to very small and localized tumor. Frameless immobilization systems SRT delivery can facilitate with frameless immobilization system and are less invasive for the patient. Although, this type of immobilization is less rigid, patient positioning may differ from day to day. A challenge of this immobilization system for inter- and intra-fraction uncertainties is incorporating them into the treatment plan. Therefore, multiple fractions, geometric uncertainties are associated with daily patient immobilization and isocenter alignment. Hence, the margin required from these geometric uncertainties to get the intended dose to target while minimizing dose to surrounding tissues. The successful delivery of SRT is promoted by image-guided radiation therapy (IGRT), leading to a larger biologically effective dose received by the target[8]. Therefore, SRT treatment needs very accuracy and precise treatment.

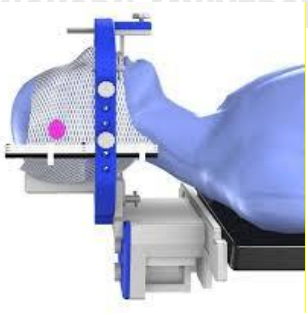


Figure 2. 3 Patient immobilization device with mask for SRT treatment

2.1.4 Radiotherapy Treatment Planning

Developments of technology in radiation therapy was increased in 1990s, especially computer technology which initiated to plan radiotherapy dose in three dimensions, led to the recognition that concise definitions of both the primary tumors

and possible areas of local spread were required. As well as the system of planning in radiotherapy are popular for individual patients, target volume determinations are essential for radiotherapy protocols because the uniformity of planning is needed to allow when comparing the reporting of results in multi-center trials and different centers. Treatment planning is the method that consists of contouring, arrangement of the consideration of beam direction, plan optimization, 3D images such as CT and MR images are used for basic dose calculation and plan evaluation with dose volume histogram. Usually, the CT is the gold standard images for radiotherapy planning since they provide the accurate patient contouring, and difference value of Hounsfield unit (HU) related to electron density for radiation dose calculation. Moreover, inhomogeneity correction for the accurate dose calculation in EBRT is required the different HU.

2.1.5 Volume definition

Target volume and critical structure definition are reported by International Commission on Radiation Units and Measurements (ICRU) reports no. 50 and 62. The following volumes have been defined as principal volume related to 3D treatment planning gross tumor volume (PTV). In SRT, small brain lesions are treated with GTV and small GTV to PTV margins in few fractions. The steep dose gradients are required around the PTV to avoid damage to surrounding organs, mainly the central nervous system due to the relatively high dose per fraction[9]. As target localization uncertainty should be very small (typically within 1 mm) in SRT, local control of treatment is very important and need to minimize the risk of injury to the surrounding brain tissue. Therefore, adequate patient immobilization is the main consideration in SRT. Todays, special thermoplastic stereotactic masks are commonly used for SRT treatments.

2.1.6 Volumetric Modulated Arc therapy (VMAT)

Volumetric modulated arc therapy (VMAT), an advanced form of intensity modulated radiation therapy (IMRT), is a novel treatment planning technique that use the inverse planning optimization concept to create dose distribution[1]. For multiple brain metastasis, non-coplanar arcs are commonly used in beam arrangement to increase the more conformal dose distribution and the simultaneous variation of multi-leaf collimator positions, dose rate, and gantry speed during treatment delivery are performed to modulated the intensity of the beams[1, 10]. Compared with IMRT, VMAT presents the efficient treatment delivery that gives in very short time. VMAT has been used for based SRT for multiple targets to be treated simultaneously using single plan with single isocenter as shown in Figure 2. 4. In clinical, the VMAT optimization depends on the selection of difference plan parameters, such as the number of arcs, the delivery time, or the gantry angle speed. The multiple non-coplanar arc VMAT consistently provides accurate and high dose distributions with low doses to healthy brain tissue and high dose conformity to the target. These factors are suitable for larger and more irregular shape of lesions. For smaller and rounder lesions, fewer couch angles or arcs lead to reduce treatment times[11].

Figure 2. 4 VMAT SRT treatment by standard linac machine

2.1.7 Stereotactic Radiation therapy (SRT)

Stereotactic radiosurgery (SRS) refers to the use of a three-dimensional coordinate system (stereotactic) to deliver high dose radiation in single fraction, give very high dose to tumor especially gross tumor volume (GTV) of focal radiation to intracranial targets with submillimeter localization in a noninvasive manner (radiosurgery) as a substitute for surgery while avoiding irradiation of the surrounding healthy tissue due to rapid fall off dose. Stereotactic radiotherapy (SRT) is same as SRS but SRT performs small fractionation treatment such as 2-5 fractions. Therefore, SRS/SRT can define as the words of knifeless surgery. However, the toxicity of SRS with a single fraction increases risk of neurological morbidity [12, 13]. Minniti G et al[12] found that patients who were treated with SRS increase the neurological complications and suggested to consider hypofractionated stereotactic radiotherapy (HFSRT) to minimize the risk of symptomatic radionecrosis. It had been reported that HFSRT was effective to treat brain metastases, associated with better local control and reduced risk of radionecrosis as compared to SRS. Hence, SRT have emerged as the major role of treatment and important modality for multiple metastases and small targets[1]. SRT may be considered to improve radiobiological therapeutic ratio. The profits of SRT over SRS is sparing of normal tissue by improving the radiobiological ratio while maintaining the benefits of high dose per treatment [8].

2.1.8 Gamma Knife (GK) SRT vs linac SRT

There are different types of machine to treat multiple brain metastases, which are gamma knife (GK) and linac. GK and linac machines have been used for SRT that are treated with multiple brain metastases. However, GKRT has some limitations for other parts because it can use only for brain and head and neck treatment. Additionally, it uses rigid fixation that is inconvenience for patient. Moreover, many researchers compared single isocenter VMAT SRS by LINAC and GK for multi-targets. The result showed that VMAT based on LINAC was higher conformity index (CI) than GKRT [14, 15].

2.1.9 Coplanar and non-co-planar VMAT plan

VMAT SRT can plan by co-planar arc on one plane and non-coplanar arc on oblique plane with single or multi-isocenter for brain metastases. Treat on one plane

without use couch rotation that called coplanar as shown in Figure 2. 5 (a) and second, non-co-planar arc are shown in figure 2.5 (b), which can treat on oblique plane by using couch rotation. The use of multiple non-coplanar arcs at different couch angles is a technique for treating intracranial lesions that maintaining the high dose conformity in and larger lesions and/or concavities. It is expected that the use of multiple noncoplanar for cranial lesions could provide a mean of further avoiding organs at risk and minimizing the dose to healthy brain without compromising the high dose conformity of the single arc technique. However, the high number of couch rotations exactly increases the total treatment time to potentially unfavorable length.

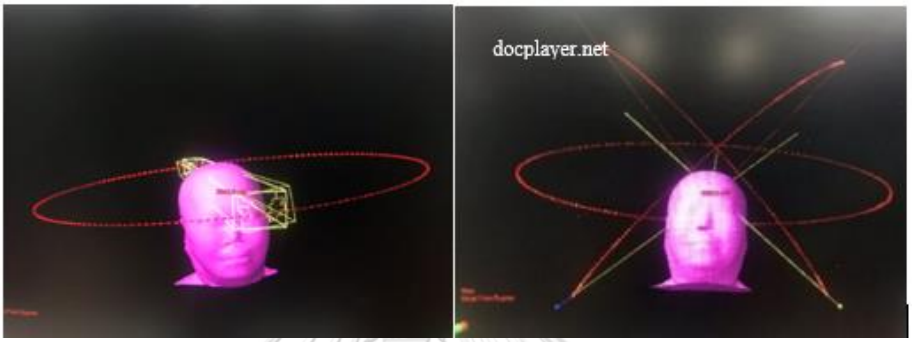


Figure (a) **Figure (b)**

Figure 2. 5 (a) one plane by co-planar arc for SRT VMAT and **(b)** oblique plane by non-co-planar arc for SRT VMAT

2.1.10 Gamma Evaluation

The Gamma Index is essential to estimate point-by-point difference between measured and calculated dose distribution in terms of both Distance to Agreement (DTA) and Dose Difference (DD). The distance between reference point and closest data point in the compared dose distribution that manifests the same dose is defined as DTA[16]. The composite analysis of DTA and DD is needed to work in both high and low dose gradient regions because DTA measure performs well only in high dose gradient regions. When passing both DD and DTA criteria, the test is passed. Moreover, the patient plan is accepted when the index value is ≤ 1 by its formula and when γ value is greater than one, plan is rejected[17]. Measured dose distributions were compared with the calculated ones using the gamma index method by applying the global normalization at 3%/2mm according to AAPM TG-218 and acceptance criteria in this study was set at 90% pass. Thus, the percentage of dose points was measured that satisfy acceptance criteria can determine the goodness of treatment plan. The gamma method, as prepared by Low et al.[18], was designed for the two dose distribution comparison: one is defined to be the reference information ($D_r(r)$) and the other is queried for evaluation ($D_c(r)$).

Figure 2. 6 represents a schematic of the gamma analysis tool for two-dimensional dose distribution evaluations. The acceptance criteria are denoted by ΔD_M for the dose difference and Δd_M for the distance to agreement (DTA). For a

reference point at position r_r, receiving dose D_r, the surface representing these acceptance criteria is an ellipsoid defined by equation 2.1.

(2. 1)

$$\Gamma = \sqrt{\frac{\Delta d^2}{\Delta d^2_M}} + \sqrt{\frac{\Delta D^2}{\Delta D^2_M}}$$

where $\Delta r = |r_r - r_c|$ is the distance difference between the reference and compared point and $\Delta D = D_c(r_c) - D_r(r_r)$ is the dose difference at the position r_c relative to the reference dose D_r in r_r. For the compared distribution to match the reference dose in r_r, it needs to contain at least one point (r_c, D_c) lying within the ellipsoid of acceptance, i.e. one point for which:

$$\Gamma_r(r_c, D_c) = \sqrt{\frac{\Delta d^2}{\Delta d^2_M}} + \sqrt{\frac{\Delta D^2}{\Delta D^2_M}}$$

A quantitative measure of the accuracy of the correspondence is determined by the point with the smallest deviation from the reference point, i.e. the point for which $\Gamma_r(r_c, D_c)$ is minimal. This minimal value is referred to as the quality index $\gamma(r_r)$ of the reference point.

The pass-fail criterion therefore becomes:

$\gamma(r_r) \leq 1$, correspondence is within the specified acceptance criteria,

$\gamma(r_r) > 1$, correspondence is not within specified acceptance criteria.

An implicit assumption is performed that once the passing criteria are selected, DD and DTA analyses have equivalent significance when determining calculation quality.

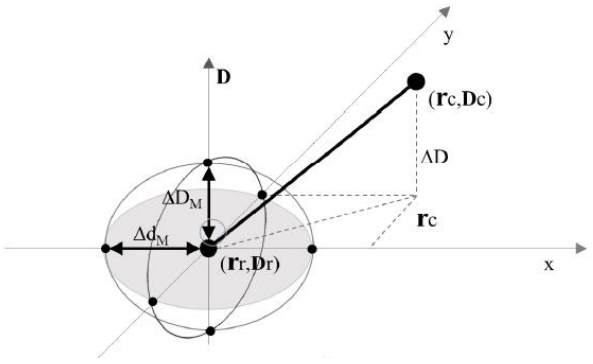


Figure 2. 6 Schematic representation of the theoretical concept of the gamma evaluation method

2.1.11 Planning Evaluation

Quantitative analysis of the VMAT plans was performed using cumulative dose-volume histogram. Evaluation of the quality of the treatment plan was quantitatively

assessed in terms of $CI_{PADDICK}$, $GI_{PADDICK}$, HI_{ICRU}, and mean dose to normal brain, V_{6Gy}, and V_{12Gy}.

2.1.12 Conformity Index[1]

Paddick CI was defined as the ratio of the dose of prescribe volume to target volume as shown in equation**(2. 2** 2.2.

(2. 2)

$$\text{Paddick CI} = \frac{(\text{TV}_{PV})^2}{\text{TVXPV}}$$

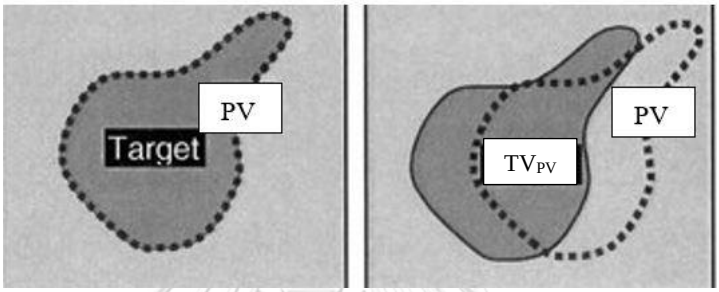


Figure 2. 7 Definition of the volume used in coverage and conformity parameters

where, TV_{PV} is target volume within the prescribed isodose surface, TV is target volume and PV is prescribe dose volume. Figure 2. 7 describes the definition of the volume used in coverage and conformity parameters.

CI value should be the range between 0 and 1. The ideal plan would have a CI value close to unity. The lower CI presents the poor the conformity.

2.1.13 Gradient Index[1]

Paddick GI was defined as the ratio of half of the dose prescription volume to prescription volume (PV) as shown in equation 2.3.

(2. 3)

$$\text{GI}_{\text{Paddick}} = \frac{\text{PV}_{50\%}}{\text{PV}}$$

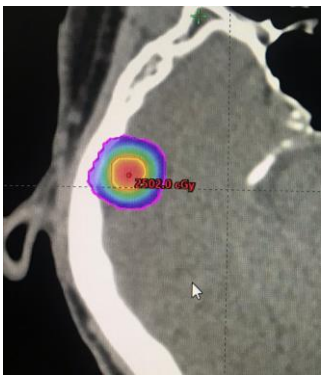


Figure 2. 8 Definition of rapid fall off dose outside GTV and gradient index parameter

where, $PV_{50\%}$ is the 50% of the prescription dose volume and PV is prescription dose volume. Figure 2. 8 illustrates GI is the rapid fall off dose outside GTV and generally should be less than 3 for single target SRT.

2.1.14 Homogeneity Index[19]

Dose homogeneity was assessed using the International Commission on Radiation Units and Measurements (ICRU) homogeneity index (HI_{ICRU}) as defined in ICRU 83[20] as the maximum dose delivered to 2% of target volume ($D_{2\%}$) and the minimum dose to 98% of target volume ($D_{98\%}$) divided by median dose ($D_{50\%}$).

(2. 4)

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{median}}$$

Smaller value of HI value corresponds to more homogenous irradiation of target of volume. A value of zero corresponds to absolute homogeneity of dose within target.

2.1.15 Treatment field verification with kV CBCT

SRT VMAT technique is used to precisely define the target and accurate treatment planning with shaped beams in iso-centric or non-isocentric geometry. Therefore, IGRT is contributed as an essential role to verify patient position and improve the accuracy of treatment with the commonly used by kilovoltage cone beam computed tomography (kV CBCT) before radiation dose delivery. It is beneficial tool to assess patient position before treatment delivery since it provided the 3D information, organ variation and patient movement in treatment. On the other hand, radiation technologists are able to observe the patient anatomy during the course of treatment and consequently can decide for adaptive radiotherapy planning. This IGRT shows the vital roles to manage and notice the movement of the internal structures. It may impact on the accuracy of high radiation dose to target volume and all nearby OARs particularly in SRS, SRT.

2.2 Literature Reviews

Clark GM, et al.[1] studied in feasibility of single-isocenter VMAT SRS for treatment of multiple brain metastases and compared single and multi-isocenter technique. The purpose of this study was to evaluate the relative plan quality of single-isocenter and multi-isocenter VMAT for radiosurgery treatment of multiple central nervous system metastases. This study had simulated images of 4 patients with created 3 lesions per each plan by varying with different size and 3 cm vs 6 cm distance for each lesion. They compared three planning techniques, which were single-arc single-isocenter (SASI), triple-arc single-isocenter (TASI), triple-arc triple-isocenter (TATI) by varying sizes and two equal distances between each target. The plan qualities were evaluated by DVH, Paddick CI, RTOG CI, Paddick GI for PTV, and V_{12Gy} isodose volume for normal brain. The results showed that, single isocenter VMAT was equivalence conformity to multi-isocenter. Single isocenter was not only the same conformity but also relatively reduce treatment delivery time than multi-isocenter. Whether single or multiple noncoplanar arcs with a common isocenter depended on the number and proximity of the tumors. They showed that VMAT radiosurgery for multiple targets can be extremely efficiently delivered and likely replaced multi-isocenter techniques for linear accelerator-based treatment of multiple targets.

Jay Morrison[10] investigated that a single isocenter was enough for modulated arc therapy radiosurgery when multiple intracranial metastases were spatially dispersed. The aims of this study were to determine whether improved dosimetry for spatially dispersed targets using 2-3 isocenters and investigated the effect of maximum dose constraint during optimization and dosimetric effect of the number of arcs used for large number of targets, which are 7 to 9 targets. Fifteen cases of multiple brain metastases were planned by 4 VMAT arcs and 10 VMAT arcs for single and multi-isocenter, respectively. The limitation of single isocenter such as multiple targets, distance of target and larger number of targets are needed to solve by using multiple non coplanar in other studies. So, it was found that the number of arcs needed to achieve optimal plan quality. The result described that improvements of multi-isocenter technique were modest and not statistically significant compared with single-isocenter and dose statistics were minor improvement beyond 4 arcs. Therefore, they concluded that single isocenter was likely enough for VMAT radiosurgery of multiple brain metastases.

Andrew A. Kanner,[21] evaluated a single-isocenter radiation approach to treat multiple BM with SRS technique by impact of lesion number, location and volume on treatment in VMAT planning. Ten patients with multiple BM were planned with single isocenter arc based VMAT and multiple static beams VMAT plan were generated by utilizing single isocenter with 2-5 arcs planning template. The Paddick CI, GI were applied to evaluate the PTV results, while the brain volume receiving 12 Gy was used as evaluation tools for normal brain. VMAT plans with varying dose prescribe for multiple BM showed the comparable dosimetric coverage as static beams plan but obtained with faster delivery time. They also found that VMAT

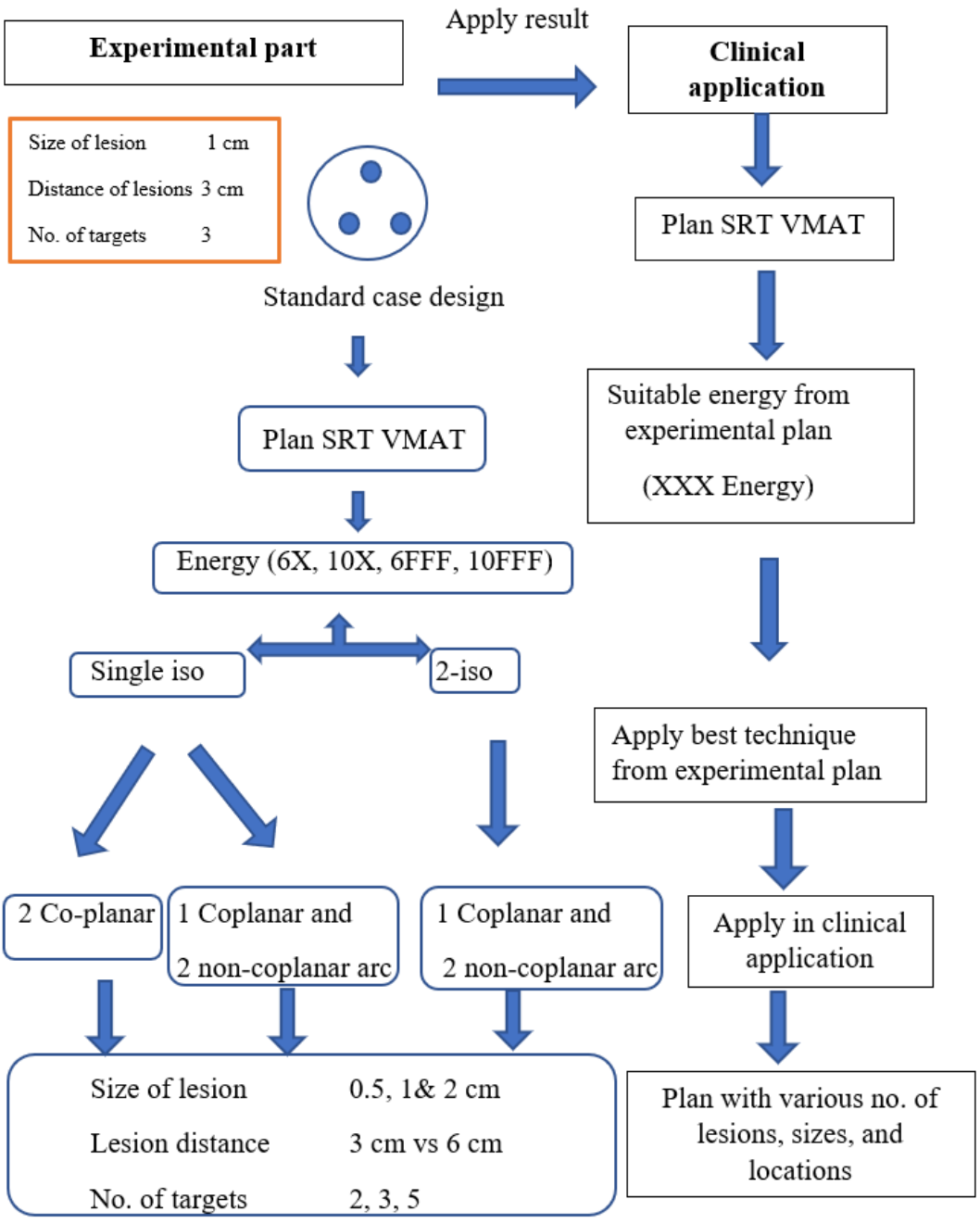
optimization process might be advantages for irregular and very long or narrow targets shapes.

CHAPTER III

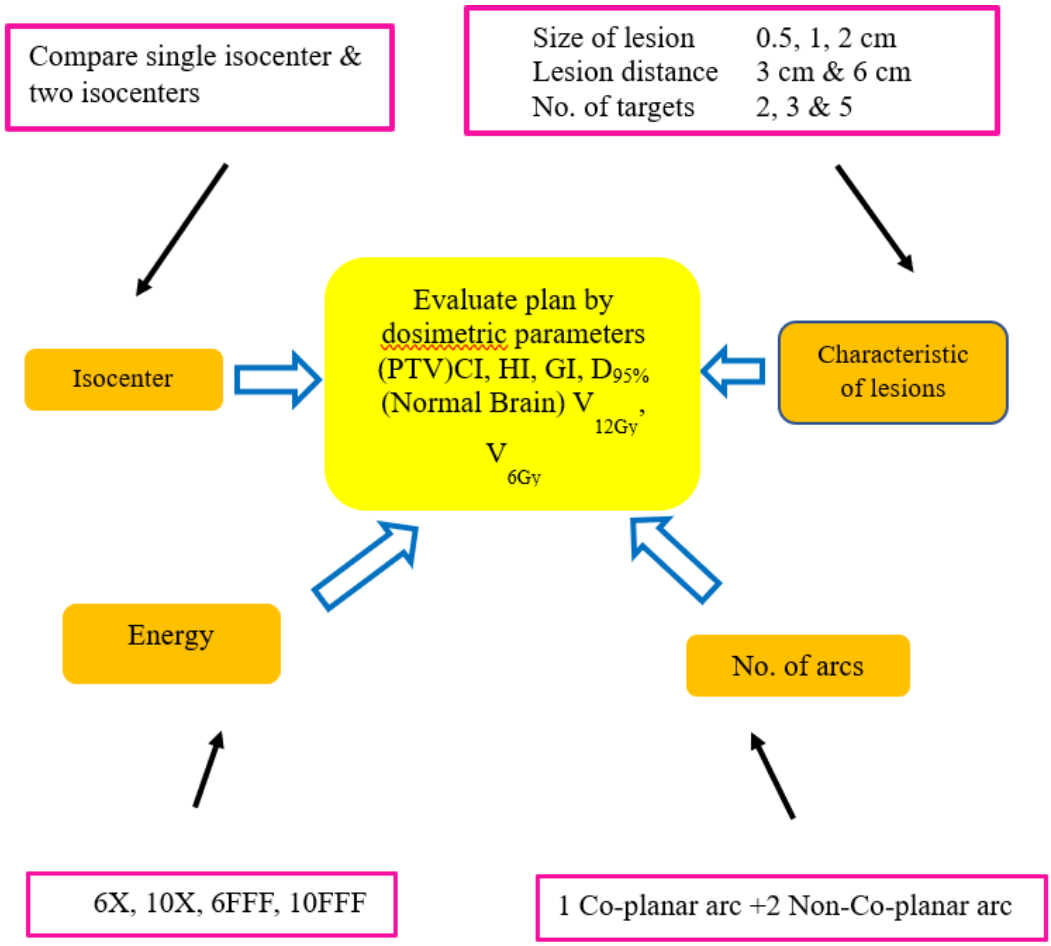
3.1 Research Design

This study is divided into two parts. The study of first part is experimental that create various types of simulation target and second part is clinical situation as observational, descriptive study with retrospective from brain metastases cases.

3.2 Research Design Model



3.3 Conceptual framework



3.4 Research question

What are the dosimetric effects between single and double isocenters SRT VMAT by various lesion number, locations, and sizes?

3.5 Materials

The materials used in this study were supplied from the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital.

3.5.1 Linear accelerator

This study used Varian TrueBeam linear accelerator with 120 MLC (Varian Medical System, Palo Alto, CA, USA), as shown in Figure 3. 1. It can be used for external beam radiation therapy treatment of cancer patient that deliver photon beams and electron beams to the treatment of the region of interest. The machine can be operated in 6MV, 10MV, 6FFF and 10FFF for photon beam and 6, 9, 12, 16 and 20 MeV for electron beams. The range of field sizes is from 0.5x0.5 cm^2 to 40x 40 cm^3 at

isocenter. The dose rates are ranged from 100 to 600 MU/min for conventional mode with flattening filter and maximum dose rate of 1400 MU/min for 6FFF, and 2400 MU/min for 10 FFF. The distance from target to isocenter is 100 cm. The 6FFF and 10FFF energies were selected in this study.

Figure 3. 1 Varian TrueBeam Linear Accelerator

3.5.2 Eclipse treatment planning system (TPS) with Anisotropic Analytical Algorithm

Eclipse treatment planning software version 15.0 (Varian Medical System, Palo Alto, CA, USA) is a treatment planning for all kinds of treatment, including 3D conformal, IMRT, VMAT, electron beams, proton beams and brachytherapy. The planning system has two types of dose calculation algorithms, which are Analytical Anisotopic Algorithm (AAA) and Acuros XB algorithm. In this study, AAA with the grid size of 1.25 mm was used to calculate for evaluation of dose distribution. This algorithm supports fast and accurate dose calculation for clinical photon beam. In addition, it can provide with high degree of tissue heterogeneity by accounting for the 3D density variation directly in the dose calculation. The Eclipse software is illustrated in Figure 3. 2.

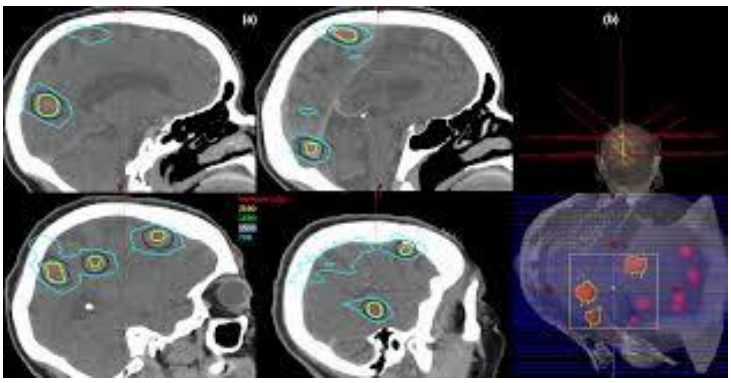


Figure 3. 2 Eclipse treatment planning software version 15.0

3.5.3 Arc CHECK 3D diode arrays

A new 3D diode arrays (ArcCHECK Sun Nuclear, Melbourne, FL, USA) system has been developed for routine QA verification of IMRT, and VMAT[22, 23]. Then, VMAT treatment delivery gives in very short time and gets accurate and precise treatment. The ArcCHECK is made of cylindrical water-equivalent phantom with a three-dimensional array of 1,386 diode detectors with 10 mm detector spacing[24]. The device geometry is cylindrical, which detectors are always facing with the delivery beam according to the gantry angle and measure entry and exit dose for every angle. The detectors spiral down the cylinder with dimensions of 21 cm diameter and length in order to increase the spatial sampling rate and reduce detector overlap from the beam's eye view (BEV). The active detector size is 0.8×0.8 mm^2 and 15 cm diameter cavity in the phantom that can hold an insert with an ionization chamber to measure absolute dose. The ArcCHECK measures in 50 ms intervals, saves all measurement data as a function of time, and performs both relative and absolute dose measurements[24]. The system can assess the accuracy of MLC positions and the dose rate at each control point, as well as the gantry speed between control points at the same time[25]. Many studies have been performed to commission and characterize the Arc CHECK device, and it has been evaluated that the short-term reproducibility, dose linearity, dose rate dependence, dose per pulse dependence, field size dependence, and out-of-field dependence of ArcCHECK are suitable for IMRT and VMAT QA[26]. The ArcCHECK gives a higher confidence in terms of gamma comparison between measured and calculated dose distribution[27]. This device is also MRI compatible and was used for IMRT QA in MRI-guided RT[28].

3.5.4 Sun Nuclear Patient software

In the advanced treatment technique such as IMRT and VMAT, the patient specific QA is the main enrollment to verify the TPS and beam delivery errors. SRS/ SRT plan consist of the collections of small beamlets and very steep dose gradients. As for highly steep dose gradients are tightly conformed to patient anatomy and PTV, an accurate verification of dose gradient is critical. Therefore, SNC patient software (Sun Nuclear Corporation, Melbourne, FL, USA) compare not only to measure dose points to planned dose points but also compare the normalize data or absolute dose

data by using DTA, gamma and gradient compensation. Moreover, it can perform the plane or volume dose difference with a single click. It can review individual control points and user-defined full or sub-arc sections for an in-depth overview of pass, low, and high dose results in terms of gamma passing rate. Arc CHECK directly connects to Sun CHECK for improved root-cause analysis. It provides true data on plan delivery and insights into potential errors. The beam eye view (BEV) for all gantry angles measuring entrance and exit dose at multiple depths are consistent and indicating potential delivery and TPS modeling errors for high or low dose levels. It includes real-time electrometer that measures every pulse, as well as composite and sub-arcs. The SNC software and Arc CHECK phantom are shown in Figure 3. 3 (a) and (b), respectively.

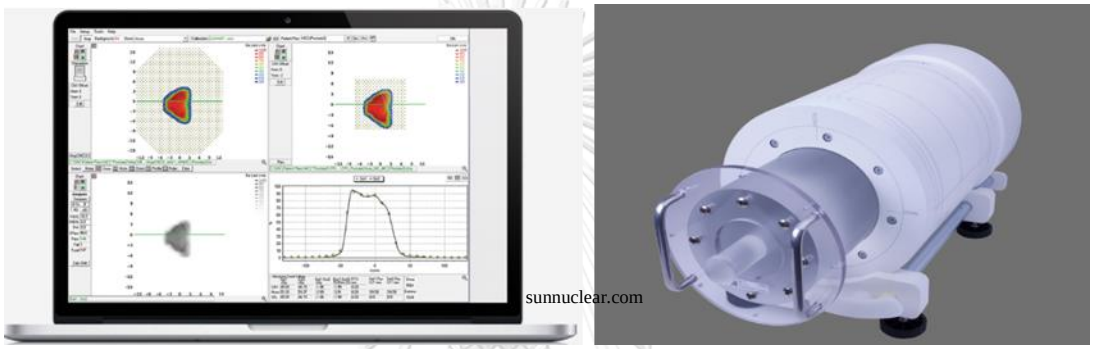


Figure 3. 3 (a) Sun Nuclear Corporation patient software **(b)** ArcCHECK phantom

3.6 Methods

3.6.1 Patient selection

This study is divided into two parts. The first part of study was experimental that create various types of simulation target with 18 plans and second part was clinical situation as observational, descriptive study with retrospective from brain metastases cases. As clinical part, ten patients plan with brain metastasis that were treated with SRT techniques at King Chulalongkorn Memorial Hospital during 2016 to 2018 were randomly enrolled.

3.6.2 Experimental parts of study

1) The patient data that already completed course of SRT treatment was investigated and the collected data was average to simulate the standard case such as lesion size, number, and distance of each lesion.

2) The standard lesions which were 1 cm for all lesion sizes, 3 cm distance for each lesion and 3 lesions number were created on planning non-contrast CT image.

3) The PTVs were contoured on non-contrast CT simulation image in each case by researcher. GTV are commonly used for SRT cases without PTV and CTV because of strict for patient immobilization. However, one PTV was used for multiple lesions as combination of GTVs in this study.

4) In the part of energy selection, the VMAT SRT plans were conducted with varying the energy of 6X, 10X, 6FFF and 10FFF using 3 techniques which are single isocenter for 2 coplanar arc, 1 coplanar combine with 2 non-coplanar arcs, and 2-isocenter for 1 coplanar and 2 non-coplanar arc. Each energy was applied to three techniques and total of 12 plans were performed.

5) As the selection of treatment planning techniques, 3 techniques were compared by varying lesions size, number, and distance apart each other. When each variation was performed, other parameters were fixed. All simulated patient plans, regardless of the isocenter or number of arcs, were planned with optimization dose of 21 Gy in three fractions. Anisotropic Analytical Algorithm (AAA) was used for dose calculation and plans was normalized to deliver 100% prescribe does to 95% volume of PTV.

6) VMAT SRT plans were optimized on original treatment plan image by Eclipse Treatment Planning System version 15 and the same optimization parameters were applied for all plans. Re-planning from single isocentre plan to double isocentre plan were performed with same optimization criteria. Eighteen VMAT SRT plans were generated with varying lesion sizes, numbers and distance apart each using 3 beam arrangement techniques, which are single isocentre for 2 coplanar arc, single isocenter for 1 coplanar combine with 2 non-coplanar arcs, and double isocentres for 1 coplanar and 2 non-coplanar arc per isocenter. The machine of Varian TrueBeam linac with 120 MLC was selected in planning.

7) The plans were analyzed by evaluation tools which were CI, GI, and HI to specify energy, isocenter and number of arcs by varying number of lesions, sizes, and distance from each lesion.

3.6.3 Planning Techniques

The parameters as shown in Table 3. 1 are the summarized of three planning techniques (2 Arcs SI, 3 Arc SI, and 6 Arcs DI) for arc geometry setting up in both coplanar and non-coplanar techniques.

3.6.3.1 The 2 Arcs single isocentre (2 Arcs SI)

The 2 Arcs SI was performed by 0° couch angle, 2 full arc co-planar, which the gantry angle was full rotation from 179° to 181° with both counterclockwise (CCW) and clockwise (CW) directions. To prevent interleaf leakage, the collimator angle was set at 355° and 5° for CCW and CW, respectively.

3.6.3.2 The 3 Arcs single isocentre (3 Arcs SI)

The 3 Arcs SI was set the angle of couch rotation at 0°, 45° and 315° for each respective arc to perform two non-coplanar arcs. The gantry angle was set one full coplanar arc with 179° to 181° CCW and combined 2 half non-coplanar arc with gantry angle from 150° to 30°(CCW) and 210° to 330°(CW) with collimator angle of 5°and 355°, respectively.

3.6.3.3 The 6 Arcs double isocentres (6 Arcs DI)

The 6 Arcs DI was planned with couch angle, gantry angle and collimator rotation the same setting as 3 Arcs SI plan, but 3 arcs per each isocentre were set.

Table 3. 1 Arc geometry by couch rotation, gantry angle and collimator rotation

Plan	Gantry start angle	Gantry stop angle	Gantry direction	Couch angle	Collimator angle
2Arcs SI	179	181	CCW	0	355
	181	179	CW	0	5
3Arcs SI	179	181	CCW	0	355
(6Arcs DI)	150	30	CCW	45	5
	210	330	CW	315	355

3.6.4 Plan Evaluation and comparison

VMAT SRT plan was performed by cumulative dose volume histogram (DVH) that referred to plan quality evaluation with Paddick CI, Paddick GI, and ICRU HI for PTV. The volume of received dose of 6 Gy and 12 Gy (V_{6Gy}, V_{12Gy}) were recorded for normal brain and total monitor unit (MU) was also collected. For dosimetric comparison, the indices for PTV were used as follows:

3.6.4.1 Plan evaluation by DVH

The goal dose is the dose to 95% of PTV volume, which are achieved at prescription dose. The minimum dose or D_{min} is dose to 98% of PTV volume, which should be received more than 98% of prescription dose. The maximum dose or D_{max} is dose to 2% of PTV volume, which should not be received more than 110% to 120% of prescription dose in SRT case. The dose to organ at risk or critical organ should not be received more than a tolerance dose. Normal tissue is defined as the organs surrounding and outside the PTV. In this case, normal brain was considered. The 12 Gy isodose volume (V_{12Gy}) defined as the volume that received 12 Gy isodose and 6 Gy isodose volume (V_{6Gy}) of brain defined as the volume that received 6 Gy were record as a normal tissue volume dose.

3.6.4.2 Plan evaluation by dose statistic indices

Conformity index (CI) demonstrates the conformity of dose in target volume, it is defined according to equation 2.1 the ideal value should be 1.

Gradient index (GI) demonstrates the rapid fall-off doses outside PTV, it is defined according to equation 2.2, the ideal should be 3 for SRS single target, and however, the values were higher in case of multiple targets.

Homogeneity index (HI) demonstrates the homogeneity of dose in target volume, it is defined by DVH and calculated according to equation 2.3, the ideal value should be 0.

3.6.5 Clinical part of study

The patient data that already completed course of SRT brain metastases treatment were selected.

1) The planning of CT image that included with tumors and organs contoured were set by radiation oncologist and dose distribution from VMAT SRT plan.
2) The 10 patients plan was performed by passing criteria technique and applied with various size, lesions, and location on images of original treatment plan.
3) The dose volume histograms (DVHs) were plotted, variation of the dosimetric between volumes and dose for PTV and normal brain.
4) The dosimetric and volumetric difference of PTV and organs at risk for V_{12Gy} and V_{6Gy} were analyzed.
5) After applied for 10 patients plan in clinical situation, the dosimetric plan evaluated by using $GI_{PADDICK}$, $CI_{PADDICK}$, HI_{ICRU} for PTV and V_{12Gy}, V_{6Gy} for normal brain.

3.6.6 Patient specific QA

In this study, 3D diode arrays (ArcCHECK Sun Nuclear, Melbourne, FL, USA) system has been used for measuring the dose for QA verification of VMAT SRT plan. The procedure of patient specific QA were presented as follows:

1) The VMAT SRT plans were created verification plan in homogeneous phantom as original plan and then recalculated in TPS. The data such as DICOM RT plan, DICOM RT Structure set, DICOM RT Dose (3D patient dose) were transferred to TPS.
2) The central axis of dose plane from Eclipse TPS was imported to Sun Nuclear Patient software.
3) ArcCHECK phantom was set up on the treatment couch, adjusted the phantom to make sure isocenter alignment on the three side of phantom, it is illustrated in Figure 3. 4.

Figure 3. 4 The setup of ArcCHECK phantom

4) The 2D dose plane from TPS and measurement file were compared by employing the gamma passing rate index as shown in Figure 3. 5. QA scores (percentage of dose point with a gamma value less than 1) were generated for each pairs of planes by using gamma criteria of 3%/2mm with 10% threshold dose according to AAPM TG 218 recommendation, which the passing rate should be greater than 90%.

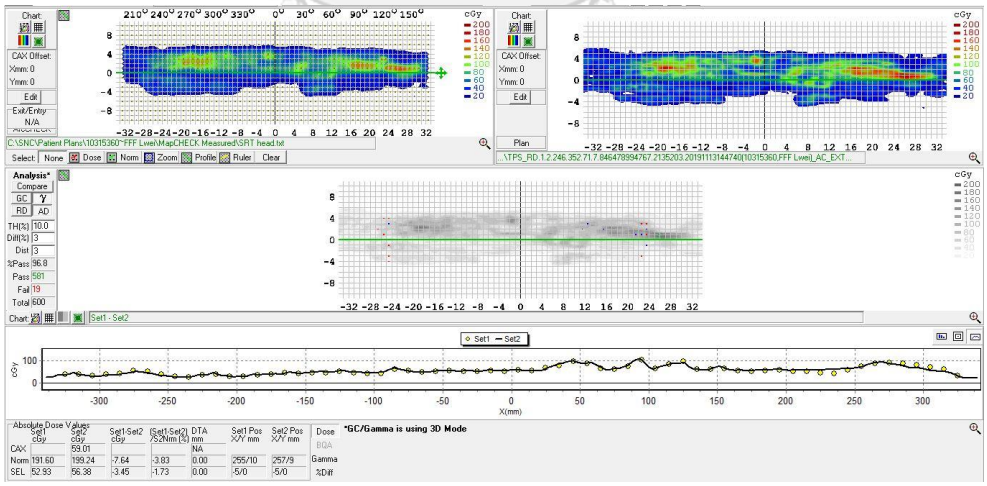


Figure 3. 5 Dose comparison between measurement and plan dose calculation on SNC patient software

3.7 Statistical analysis

The results were analyzed by average value, standard deviation (SD), percentage difference and p-value. The ANOVA was used in experimental outcomes to compare the dosimetric effect by various number of lesions, sizes, and distance by using VMAT SRT techniques and use average data and paired sample t-test and p-value with 95% confidence level.

3.8 Sample size determination

The sample size was determined using formula as equation**(**3. 1**)**;

(3. 1)

$$N = \left(\frac{Z\sigma}{E}\right)^2$$

where, Z is the value from the standard normal distribution reflecting the confidence level that will be used (Z = 1.96 for 95%); $\alpha = 0.05$, $Z_{\alpha/2} = 1.96$

N = Number of patient cases

σ = standard deviation of the outcome variable = 2.674

(from literature reviews: parameter GI)

E = the desired margin of error = 2

$$N = \left(\frac{1.96 \times 2.674}{2}\right)^2 = 6.86$$

Therefore, n is 6.86 and we need to collect minimum 7 patients.

3.9 Target Population

The patient selection criteria were set according to inclusion criteria and exclusion criteria.

3.9.1 Inclusion criteria

1) Patient data which diagnosed with brain metastases
2) Multi-targets only
3) Range of age between 40 to 60-year-old
4) Planning technique: SRT VMAT

3.9.2 Exclusion criteria

1) Primary brain tumor such as meningioma, glioma etc.
2) Over 5 lesions

3.10 Outcome Measurement

Dosimetric effects based on advanced planning of SRT VMAT as variable of tumor sizes, lesions, and distance from clinical case of multiple brain metastases.

3.11 Benefits of research

This research was helpful to obtain information that how much effective the dosimetric plan in various number of lesions, size, and distance by using SRT VMAT. It may predict which technique will be more suitable for patients with multiple targets treated by using 1-isocenter and 2-isocenter SRT VMAT plan.

3.12 Ethical consideration

This research involves the dosimetric effects between SI VMAT and DI VMAT by various lesion numbers locations and sizes. This study used images of patient from treatment planning system. The research proposal was submitted and approved by Ethic Committee of Faculty of Medicine, Chulalongkorn University, and Bangkok, Thailand (IRB NO. 268/62).

CHAPTER IV
RESULT

The results were separated into 2 parts: the experimental and clinical application of the study.

4.1 Experimental study application

4.1.1 The plan quality indices comparison of energy

The comparison of dosimetric parameters between 6MV, 10MV, 6FFF and 10FFF photon energies in 3 techniques are described details in APPENDEX A. The prescribed dose for PTV was 21 Gy in 3 fractions. VMAT SRT plans were performed with varying difference energies by 3 techniques in simulated lesions. As the average results, 6 FFF was better than other energies in terms of plan evaluation tools (GI, CI, and HI). The results showed that dose conformity (CI), dose fall off (GI) with 6FFF were better than 10FFF, 6 and 10 MV, while HI value was not much significant different among the energies. In addition, the beam-on time and MU with 6FFF, 10FFF, and 10MV were less than 6 MV. In SR TVMAT technique, many modulated beam were generated and dose rate was different with energy and depended on output rate. However, monitoring unit (MU) were not significant different for all energy (p-value: 0.17), the removal of FF increased the dose rate, shortened treatment delivery time improved the accuracy of treatment due to intra-fractional patient motion. So, 6FFF was selected to use in comparison of 3 techniques. The study of energy selection was supported by the data from average value and standard deviation (SD) as shown in Table 4. 1.

Table 4. 1 The dosimetric comparison between difference energies

Evaluation tools	6MV	10MV	6FFF	10FFF
Paddick GI	19.03±2.45	20.05±1.71	18.07±1.86	20.40±1.84
Paddick CI	0.58±0.00	0.56±0.02	0.65±0.06	0.58±0.00
ICRU HI	0.18±0.00	0.18±0.00	0.17±0.01	0.19±0.02
MU	3103±382.16	2751±491.00	2919±623.73	2528±262.23

4.1.2 The plan quality indices comparison of three techniques

The $GI_{Paddick}$, $CI_{Paddick}$ and HI_{ICRU} for variation of sizes, distances and number of PTVs are shown in Table 4. 2. The effect of PTV size variation was lesser than distance variation in $GI_{Paddick}$. The effect of size variation demonstrated that 3 Arcs SI were comparable results with 6 Arcs DI in GI (10.25 ± 6.61, 9.55 ± 5.75) and

significantly better than 2 Arcs SI (12.24 ± 7.29), while CI remains the same for all techniques. HI was slightly greater in DI (0.17 ± 0.01, 0.18 ± 0.01, 0.18 ± 0.01) than SI techniques (2 arcs: 0.19 ± 0.01, 0.19 ± 0.00, 0.18 ± 0.01 and 3 arcs 0.19 ± 0.00, 0.20 ± 0.03, 0.21 ± 0.21) in three variations of sizes, distance and number, respectively. In addition, the distance and number of lesions variation part, 3 Arcs SI (GI: 16.35 ± 7.43, 18.29 ± 3.58) and 6 Arcs DI (GI: 14.58 ± 4.55, 17.26 ± 0.49) were greater result than 2 Arcs SI for GI (21.20 ± 0.8, 20.44 ± 5.46), while CI is not significantly different in distance variation (2 arcs SI: 0.56 ± 0.03, 3 arcs SI: 0.60 ± 0.01, 6 arcs DI: 0.60 ± 0.01) among 3 gantries setting up techniques. Moreover, 3 Arcs SI is the best for CI in lesion number variation (0.58 ± 0.16). Figure 4. 2 shows the plan comparison in terms of GI according to variation of lesion sizes, distances, and numbers of lesion. It was found that non-coplanar plan improved when lesion size and distance were increased because large number of arcs can be advantageous for optimizing the dose gradient Index (GI). Although the larger number of lesions was better in DI, SI was enough in 2 lesions brain metastases. In addition, GI was decreased with the increase in target volume and was increased with the increasing of the larger lesion numbers. When the distance between targets and nearest OARs was increasing, GI was less.

Figure 4. 2 shows the plan comparison in terms of CI according to the variation of lesion sizes, distances, and number of lesions. The recommended value for Paddick CI should be between 0.6 and 1.0. The result found that CI was not significantly different for all variation. The larger target volume was, the easier to produce a conformal dose plan. ICRU HI was comparable for all techniques as shown in Figure 4. 3. When the distance between target, target volume and number of targets were increased, small amount of HI was changed.

4.1.3 Normal brain tissue

Table 4. 3 illustrates the normal brain volume at 6 and 12 Gy isodose for each technique. The 6 Arcs DI showed slightly lower normal brain volume in both 6 and 12 Gy than 3 Arcs SI, while 2 Arcs SI showed significantly higher normal brain volume in both V_{6Gy} and V_{12Gy} than 3 Arcs SI for all PTV sizes, distances, and number variations. For V_{12Gy} of normal brain, the greatest dose volume differences was found at 2 Arcs SI (31.97 ± 19.12) and 6 Arcs DI (24.50 ± 15.22), while slightly increased volume of 3 Arcs SI (25.57 ± 15.64) than DI (24.50 ± 15.22) were observed. The 2 Arcs SI plan generated a total of 6 Gy volume of 139.27 ± 70.98 cm^3, the 3 Arcs SI plan yielded 96.33 ± 36.56 cm^3 and 6 Arcs DI plan generated 88.70 ± 40.08 cm^3 in size variations. The 2 Arcs SI plan produced for total 6 Gy was larger volume than the other two in distance and number of lesions variation. When the distance between targets and total target volume were increased, V_{12Gy} and V_{6Gy} were also increased. From Figure 4. 5, V_{12Gy} and V_{6Gy} in DI was better than other two techniques but monitoring units was increased in non-coplanar DI than non-coplanar SI plan. In addition, SI was more convenience than DI in practice, therefore, the 3 arc SI was chosen to apply for clinical part. As the result, the area of low dose in brain such as V_{6Gy} and V_{12Gy} was reduced if more non-coplanar arcs were performed.

Table 4. 2 Plan evaluation for each technique according to variation of lesion sizes, locations, and numbers

Variable parameters	Lesions variable	Plan technique	Average $GI_{PADDICK}$	Average $CI_{PADDICK}$	Average HI_{ICRU}
Size	1, 1.5 & 2 cm	2 Arcs SI	12.24 ± 7.29	0.76 ± 0.06	0.19 ± 0.01
		3 Arcs SI	10.25 ± 6.61	0.71 ± 0.04	0.19 ± 0.00
		6 Arcs DI	9.55 ± 5.75	0.72 ± 0.03	0.17 ± 0.01
Distance	3 & 6 cm	2 Arcs SI	21.20 ± 0.85	0.56 ± 0.03	0.18 ± 0.01
		3 Arcs SI	16.35 ± 7.43	0.60 ± 0.01	0.20 ± 0.03
		6 Arcs DI	14.58 ± 4.55	0.60 ± 0.01	0.18 ± 0.01
Number	2, 3 & 5	2 Arcs SI	20.44 ± 5.46	0.53 ± 0.14	0.18 ± 0.01
		3 Arcs SI	18.29 ± 3.58	0.58 ± 0.16	0.21 ± 0.21
		6 Arcs DI	17.26 ± 0.49	0.54 ± 0.02	0.18 ± 0.01

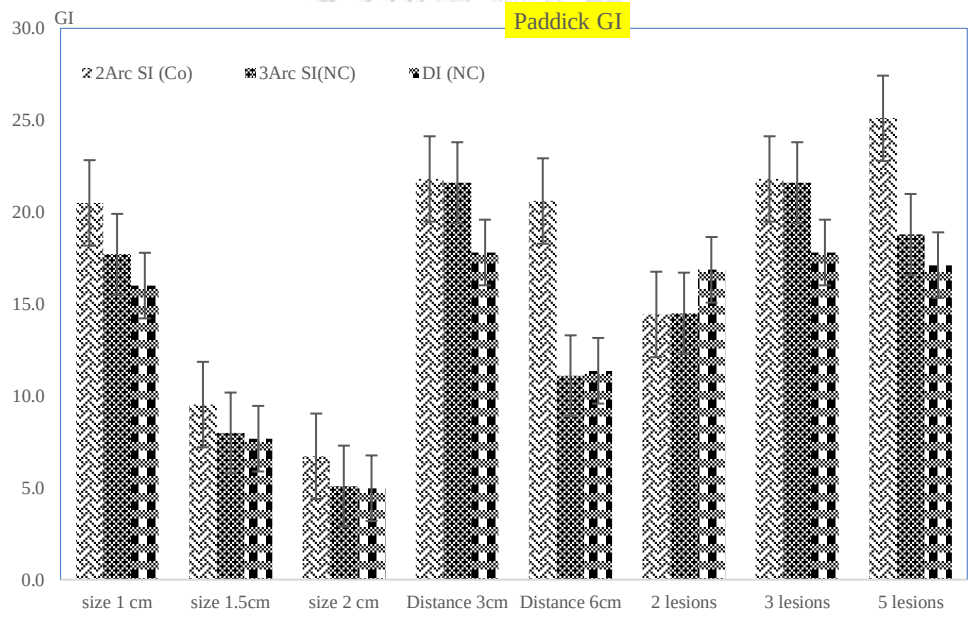


Figure 4. 1 Gradient index comparison among 3 techniques with varying lesion sizes, distances, and numbers

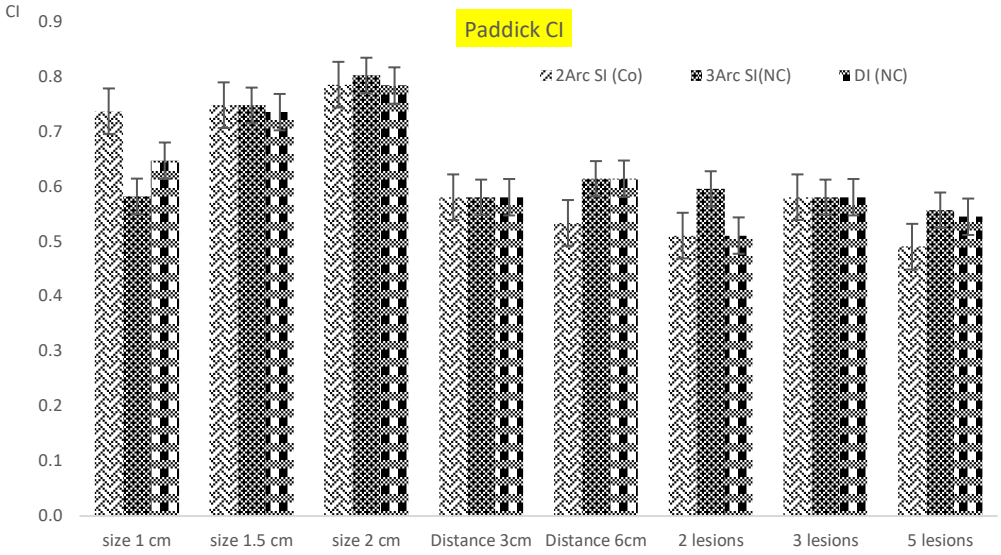


Figure 4. 2 Conformity index comparison among 3 techniques with varying lesion sizes, distances, and numbers

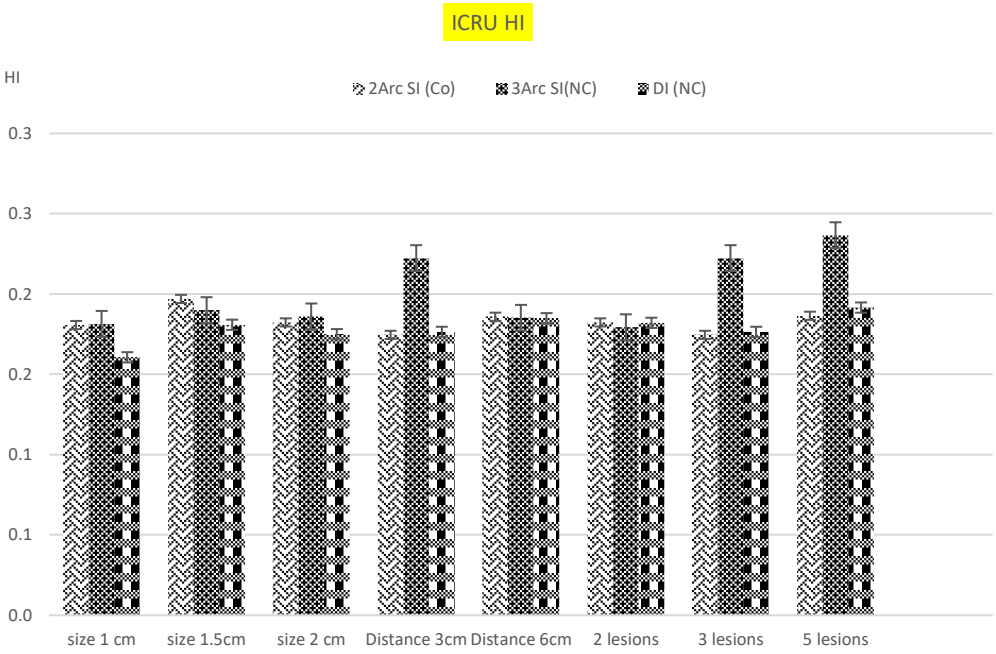


Figure 4. 3 Homogeneity index comparison among 3 techniques with varying lesion sizes, distances, and numbers

Table 4. 3 Plan evaluation of dosimetric parameters for normal brain

Variation parameters	Lesions variable	Plan technique	Average $V_{12Gy\ (}cm^3$)	Average V_{6Gy} (cm^3)	Total MU
Size	1, 1.5 & 2 cm	2 Arcs SI	31.97 ± 19.12	139.27 ± 70.98	3159 ± 585
		3 Arcs SI	25.57 ± 15.64	96.33 ± 36.56	2326 ± 127
		6 Arcs DI	24.50 ± 15.22	88.70 ± 40.08	2354 ± 162
Distance	3 & 6 cm	2 Arcs SI	13.55 ± 2.33	92.75 ± 26.80	2940 ± 508
		3 Arcs SI	11.15 ± 3.75	60.50 ± 7.50	2321 ± 309
		6 Arcs DI	9.85 ± 1.77	54.85 ± 0.21	2814 ± 166
Number	2, 3 & 5	2 Arcs SI	20.07 ± 15.87	87.23 ± 60.87	2532 ± 54
		3 Arcs SI	16.70 ± 12.41	69.83 ± 42.79	2526 ± 655
		6 Arcs DI	13.80 ± 7.43	58.57 ± 26.53	2713± 130

4.1.4 Dosimeteric comparison of 3 Arcs SI and 6 Arcs DI

Table 4. 4 The average dosimetric evaluation in all variations of three planning techniquesand Figure 4. 4 show average dosimetric evaluation in all variations of three planning techniques in term of plan quality indices. It was clear that 3 arc SI and DI were better than 2 arc SI in GI while HI and CI were comparable for all techniques. Table 4. 5 describes that $GI_{PADDICK}$ and $CI_{PADDICK}$ of two techniques; 3 Arcs SI and 6 Arcs DI, were not significantly different as supported by p value (GI_{PADDCK}; p value = 0.71, $CI_{PADDICK}$; p value = 0.83, V_{12Gy}; p value = 0.76, V_{6Gy}; p value = 0.61), while HI was significant different (HI_{ICRU} p value= 0.01). As our result, 3 Arcs SI was comparable with 6 Arcs DI. In addition, Figure 4. 6 illustrates the comparison of MU in 3 techniques that shows 3 Arcs SI and 6 Arcs DI were better than 2 Arcs SI while 3 Arcs SI was comparable with DI.

Table 4. 4 The average dosimetric evaluation in all variations of three planning techniques

Plan Technique	$GI_{PADDICK}$	$CI_{PADDICK}$	HI_{ICRU}	$V_{12Gy\ (}cm^3$)	V_{6Gy} (cm^3)	Total MU
2 Arcs SI	17.56±6.15	0.62±0.11	0.18 ± 0.01	22.90 ± 14.52	108.10 ± 57.20	2869 ± 470
3 Arcs SI	14.79±5.83	0.63±0.08	0.20 ± 0.02	18.64 ± 11.62	77.40 ± 34.30	2400 ± 390
6 Arcs DI	13.70±4.72	0.62±0.09	0.18 ± 0.01	16.83 ± 10.48	68.94 ± 30.50	2603 ± 246

Table 4. 5 Dosimetric plan comparison of 3Arcs SI and 6 Arcs DI with p value

Plan Technique	$GI_{PADDICK}$	$CI_{PADDICK}$	HI_{ICRU}	V_{12Gy} (cm^3)	V_{6Gy} (cm^3)	Total MU
3 Arcs SI	14.79±5.83	0.63±0.08	0.20 ± 0.02	18.64 ± 11.62	77.40 ± 34.30	2400 ± 390
6 Arcs DI	13.70±4.72	0.62±0.09	0.18 ± 0.01	16.83 ± 10.48	68.94 ± 30.50	2603 ± 246
P value	0.71	0.83	0.01	0.76	0.61	0.23

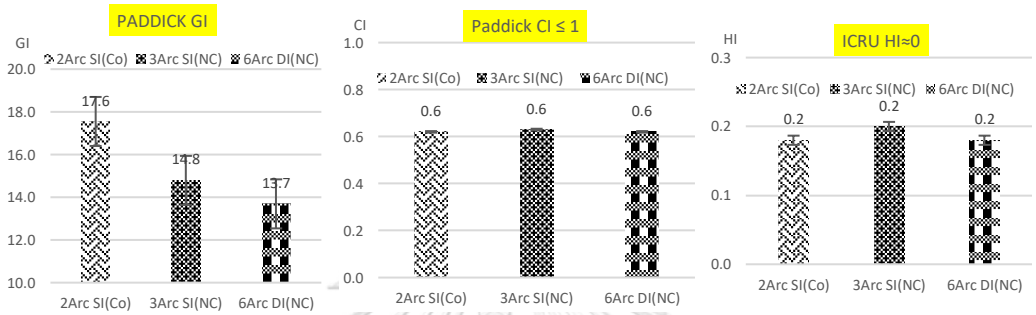
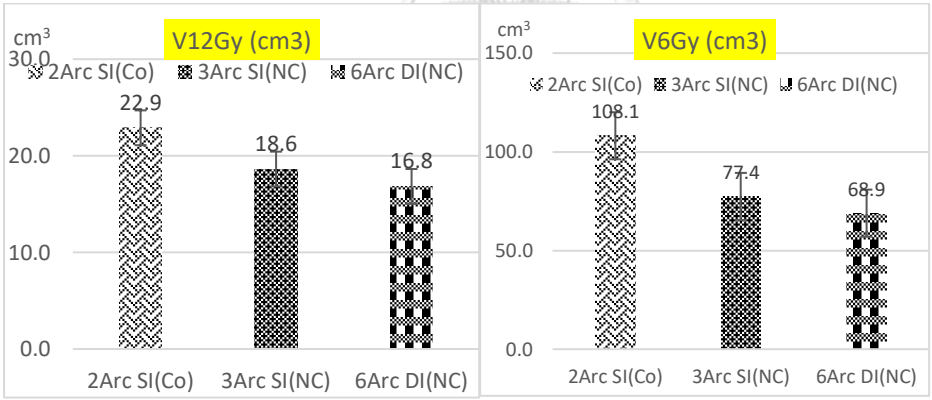


Figure 4. 4 Dosimetric plan quality indices comparison between 3 techniques for PTV



(a) (b)

Figure 4. 5 (a) Dosimetric plan comparison between 3 techniques for normal brain in 12 Gy volume and **(b)** 6 Gy volume

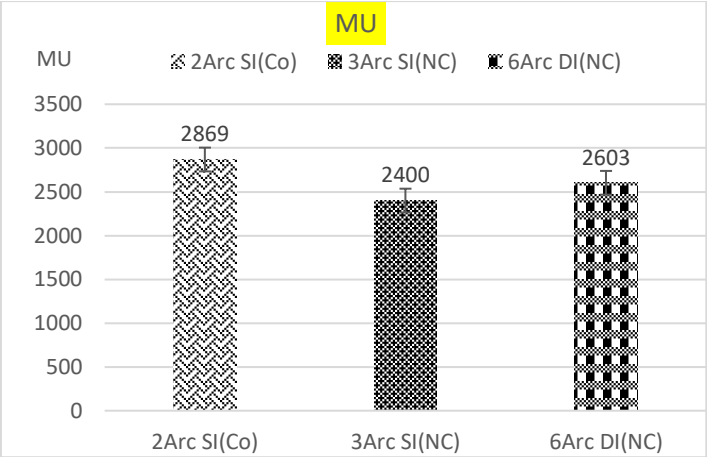


Figure 4. 6 Dosimetric comparison of total Monitoring Unit between 3 techniques

4.2 Application in Clinical patient plan

As our result, 3 Arcs SI (NC) plan was equivalent in dose fall off and conformity to 6 Arcs double isocentres (NC) VMAT. However, DI was inconvenience in practice and treatment time was also longer than SI. Therefore, 3 Arcs SI (NC) technique was selected to apply for 10 patient plans in clinical situation with multiple targets in the range of 2 to 5 targets. The results of dosimetric evaluation are shown in Table 4. 6. The multiple target volumes were in the range of 1.3 to 25.8 cm^3. The highest $GI_{PADDICK}$ value of 9.46 in patient number 8 was observed, while the other patients for GI value were around 5. The CI and HI values for all patients were quite constant with difference in actual clinical situations. When total target volume increased, the volume of 6 Gy receiving to normal brain was high as presented in case number 6 and 9.

Table 4. 6 Clinical application result by applying 3 Arcs SI (NC) technique

Patient	TV (cm^3)	No. of targets	$GI_{PADDICK}$	$CI_{PADDICK}$	HI_{ICRU}	V_{12Gy} (cm^3)	V_{6Gy} (cm^3)
1	5.4	2	5.10	0.79	0.18	20.00	88.00
2	9.3	2	4.06	0.60	0.17	28.30	96.60
3	19.8	3	3.65	0.74	0.17	53.80	173.80
4	10.5	3	4.31	0.60	0,18	32.50	132.40
5	15.1	4	4.64	0.79	0.19	50.70	261.70
6	23.6	2	5.00	0.75	0.21	89.40	315.70
7	8.6	5	5.51	0.61	0.19	34.30	197.10
8	1.3	3	9.46	0.59	0.19	8.70	43.30
9	25.8	4	4.00	0.69	0.19	75.00	322.30
10	15.6	5	4.23	0.67	0.19	48.90	246.80

4.3 Patient Specific QA

The patient specific QA for 10 plans from clinical parts were performed to verify using ArcCHECK phantom in the treatment room and results are displayed in the following Table 4. 7. The gamma criteria of 3% 2mm with 10% threshold was applied as the recommendation by AAPM TG 218. The results showed that the average percent passed were 94.0 ± 1.6 for all verification plans.

Table 4. 7 Percent pass rate measured by ARC CHECK to verify the plans

Patient number	TV (cm^3)	No. of targets	Gamma passing rate at 3%/ 2mm
1	5.4	2	92.0%
2	9.3	2	91.7%
3	19.8	3	95.4%
4	10.5	3	90.9%
5	15.1	4	94.3%
6	23.6	2	94.5%
7	8.6	5	95.1%
8	1.3	3	95.4%
9	25.8	4	95.0%
10	15.6	5	95.0%
Average ± SD			94.0± 1.62

CHAPTER V
DISCUSSION AND CONCLUSION

5.1 Discussion

There are two parts of result for discussion which are experimental and clinical applications.

5.1.1 Experimental study

5.1.1.1 Energy selection

The comparison of dosimetric parameters among 6MV, 10MV, 6FFF and 10FFF photon energies in 3 techniques were shown in Table 4. 1. The flattening filter creates beam to be flattened distribution. It reduces the beam intensity between two and four times. FFF beam that removes the flattening filter enhances the treatment delivery by increased dose rate. Increased dose rate results in shorter total treatment time, this shorter treatment time reduces intrafraction motion and provides the patient's treatment comfort. In addition, FFF beam offers other dosimetric advantages, which reduces the out of field dose as the result of reduced head scatter, leakage which lead to reduce the exposure to normal tissue to scattered dose outside the target field[29, 30]. This reduction in out of field doses may lead to minimizing the risk of radiation induced secondary malignancies. These modes are suitable for high dose treatments such as stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS). The lack of field flatness in VMAT plan is not a problem because the beam profile can be accounted for during inverse optimization. In this study, the maximum dose rate of 6FFF (1400MU/min) and 10 FFF (2400MU/min) were more than that of 6 MV and 10MV (600 MU/min). Thus, the range of dose rate modulations for VMAT optimization of 6FFF and 10FFF were superior to conventional energies. The result provided the minimizing of MU and beam on time in FFF beams. Based on those characteristics, our results showed better CI, GI, and HI with 6FFF than 10FFF, 6 MV and 10 MV while MU was not statistically significant for all energies. According to the results, it was clear that energies with free flattening filter had advantages and it could affect the decision to select suitable energy in each technique. As the comparison of FFF beam between 6 and 10, 6FFF shows slightly improved than 10 FFF because it might be depended on many factors such as modulated the beams, different dose rate and output rate with energy. As the agreement of these factors, 6FFF was selected to apply the comparison of technique selection.

5.1.1.2 Technique comparison

In the comparison of 3 beam arrangement techniques, the 3 Arcs SI (NC) plan presented the high plan quality in terms of gradient index (GI) and conformity (CI) for varying number of lesions, size, and location. The results of Figure 4. 1 and Table 4. 2 showed that GI was minimized when more arcs were used because the higher arc number increase the chance to optimize the dose. Clerk GM et al. reported that

multiple arcs produced better plan quality. They also revealed that when lesions had spaced closely together or close to critical structures, it might be effectiveness to use multiple non-coplanar arcs to generate a better GI[(1)]. Both GI value and the area of low dose in brain such as V_{6Gy} and V_{12Gy} were reduced when more non-coplanar arcs were used. However, the larger number of arcs should be trade off with the treatment time. As comparison of SI and DI, the gradient index was reduced in DI and it was more suitable in large number of lesion as well as it might give the dose precisely to each tumour for far distance lesions. On the other hand, DI does more complicated treatment planning with more monitoring unit. As our results, the 3 Arcs SI with non-coplanar technique was generated not only equivalence plan quality with DI but also reduced treatment set up error and convenience in practice. [(1)]Clark GM et al. also stated that single isocentre non-coplanar can be used to deliver instead of double isocentres in multiple brain metastases, but 3 different sizes and 3 lesions and 2 distance apart were studied[(1)]. In our study, we modified to 5 lesions and applied technique by various situations in clinical part. According to Clark GM et al. studied[(1)], the dosimetry of non-coplanar Arc with SI using VMAT with multi lesions were highly conformal and similar dose gradient by using DI with multiple brain metastases was observed. As Morrison J's[(10)] investigation, multiple isocentres did not provide substantial improved dosimetric parameters, they were 0.9% ± 12.7% in GI, 2.6% ±4.6%, in CI, and 2.6% ± 5.2% HI in distal location from each lesion for multiple targets. As their studies, DI was not significantly improved compare with SI. So, our results agreed with the studies by Clark GM [(1)] and Morrison J[(10)]. Thus, the 3 Arcs SI (NC) was selected and applied in 2-5 metastases patients in clinical part.

5.1.1.3 Low dose received with normal brain tissues

The normal brain tissues receiving low dose was evaluated in terms of V_{12Gy} and V_{6Gy}. As the average results of Figure 4. 5 and Table 4. 3, for 3 Arcs SI and 6 Arcs DI, the low dose was reduced in normal brain than 2 Arcs SI because these two techniques used non-coplanar plan which demonstrated the dose fall off advantages of non-coplanar irradiation. In addition, as the target close to critical organ or OARs, the dose falloff of non-coplanar technique was also shaper than co-planar technique[(31)]. Hence, the non-coplanar plans reduced the dose to normal brain tissues. In the comparison of SI and DI, DI was better than both techniques of SI for the effect of the distance and number of lesion variation. If distance per each lesion and lesion number were increased, dose bridge between lesions was large and it might affect the low dose received to normal brain tissues. In this situation, DI was better than SI. On the other hand, SI was enough for 2 lesions in this study.

5.1.2 Clinical application

In clinical situation, the three arcs SI plan applied for 10 patients plan by different situations. Results for plan quality indices were not statistically significant for all variation. But small lesions or total target volume produced higher GI value. The highest of GI value was shown in patient number 8 as present in Table 4. 6, while the other patients for GI value was less different. It might be because of very small

volume in this case (TV = 1.3 cm^3). Clark GM et al. reported a mean GI of 3.34 ± 0.42 for 15 VMAT plans with 1–5 targets with size ranged from 0.67 to 44.68 cm^3 [32]. In our study, the GI ranged from 3.65 to 9.46 with a mean of 5[33]. Ballangrud A et al. published that GI reduced with increasing target size. Therefore, our results agreed with the study by Ballangrud [33]. The larger volume of targets was generated for low dose that received in normal brain. Therefore, the volume of 6 Gy acquired to normal brain (315.70 and 322.30 cm^3) appeared to be the highest when the target volumes were 23.6 and 25.8 cm^3. The CI and HI values were not significant different for all patients. Thus, our study recommends to apply non-coplanar single isocentre technique for patient of 2-5 brain metastases. The results of our studies for plan qualities showed the similar result of Clark GM et al. study [1]. Phongprapun W et al. also described that conformity of plan quality in single isocentre was more improved for the patient in three lesions of brain metastases and the size and location of the lesions affect the dose conformity[34]. Patient number 8 showed lesser conformity (CI = 0.59) than the other (CI = 0.69 to 0.79) because of the smallest target volume which produced highest GI value. Audet C et al. also revealed a worse conformity index for smaller lesions than larger lesions[11], our clinical results confirmed this study.

5.1.2.1 Plan verification with patient specific QA

The patient specific QA was important process that was used in SRT VMAT plan to verify the accuracy of plan and movement of MLC by measuring point by point using ArcCHECK phantom and SNC software. The gamma criteria of 3%/2mm was used and the percent gamma pass should be over 90% in SRT VMAT case according to the recommendation from AAPM TG 218. We observed more than 95% gamma passing rate when 3%/3mm was used. Even the criteria to strict of 3%/2mm was set, the gamma passing rate was still higher than 90% (action limit). The failed point may be associated with couch speed, gantry start position, and leaf open time. It may also be possible that the process of sensitivity increased by raising the threshold of gamma passing acceptability, taking extra care in setting up the phantom and not adjusting the expected data to best fit the measurements[35].

5.2 Conclusion

The single isocentre with non-coplanar in VMAT is equivalent in dose fall off and conformity to double isocentres and it is optimal technique for treating multiple lesions of brain metastases. Therefore, single isocentre with non-coplanar in VMAT technique is recommended for 2-5 lesions metastases SRT. However, the limit of SI technique in this study is only maximum number of 5 lesions. Therefore, more lesion number should be studied for further research. As the result of patient specific QA, ArcCHECK contributes a higher confidence in terms of gamma comparison between measured and calculated dose distribution.

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APPENDIX A

Dosimetric comparison between energies with 3 techniques

Variation energy	Paddick GI				Paddick CI				ICRU HI			
	2 Arcs SI	3 Arcs SI	6 Arcs DI	Mean GI	2 Arcs SI	3 Arcs SI	6 Arcs DI	Mean CI	2 Arcs SI	3 Arcs SI	6 Arcs DI	Mean HI
6 MV	22.50	17.20	17.40	19.03	0.58	0.58	0.58	0.58	0.18	0.18	0.18	0.18
10 MV	22.40	18.36	19.40	20.05	0.58	0.53	0.58	0.56	0.18	0.18	0.18	0.18
6 FFF	20.50	17.70	16.00	18.07	0.74	0.58	0.65	0.65	0.18	0.18	0.16	0.17
10 FFF	21.80	21.60	17.80	20.40	0.58	0.58	0.58	0.58	0.17	0.22	0.18	0.19

APPENDIX B

The approval of institutional review board

Certificate approval from institutional review board (IRB) of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

COA No. 639/2019
IRB No. 268/62

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4493

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title	: DOSIMETRIC COMPARISON BETWEEN SINGLE AND DOUBLE ISOCENTERS VMAT FOR STEREOTACTIC RADIATION THERAPY WITH MULTIPLE TARGETS.
Study Code	: -
Principal Investigator	: Mrs. Wai Lwin Lwin Kyaw
Affiliation of PI	: Department of Radiology, Faculty of Medicine, Chulalongkorn University.
Review Method	: Expedited
Continuing Report	: At least once annually or submit the final report if finished.

Document Reviewed :

1. Research Proposal Version 2 Date 4/06/2019
2. Protocol Synopsis Version 1 Date 11/04/19
3. Case Record Form Version 1 Date 05/04/2019

Approval granted is subject to the following conditions: (see back of this Certificate)

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