

Feasibility of Large Multi-Leaf Collimator in Stereotactic Radiosurgery/ Stereotactic Radiotherapy: A Single Center Experience

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ABSTRACT

OBJECTIVE This study investigated the feasibility of using a large multi-leaf collimator (MLC) in a C-arm based linear accelerator for stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT).

METHODS Patient Specific Quality Assurance was conducted on 69 patients treated with a single lesion SRS/SRT measuring dose distribution using patient-specific plans with SRS MapCHECK®. Statistics were used to analyze the significance of correlation among dosimetric parameters, included Conformity Index (CI), Gradient Index (GI), plan complexity, and Gamma passing rate (GPR) in an absolute dose (AD) and relative dose (RD). confidence limit (CL) was also calculated to evaluate the performance of a large multileaf collimator (MLC) in SRS/SRT.

RESULTS Planning target volumes (PTVs) ranged between 0.34 cm³ and 30.42 cm³. The study found a value of CI_{ICRU}, CIPaddick, and GI of 1.29 ± 0.17, 0.77±0.10 and 5.24±2.18 (mean±SD), respectively, significant correlations were found between PTV sizes and dosimetric parameters. Values of GPR_{2%/2mm} were 92.42±3.74 (AD), 96.38±3.24 (RD), whereas GPR_{2%/1mm} were 82.03±6.69 (AD), 89.64±7.26 (RD). No significant correlation was found between plan complexity and GPR. CL values were 85.09% (AD), 90.03% (RD) for GPR_{2%/2mm} and 68.92% (AD), 75.41% (RD) for GPR_{2%/1mm}.

CONCLUSIONS This study assessed the feasibility of using a large MLC for a single lesion SRS/SRT across various PTV sizes. The values of CI and GI decreased for a small lesion. While the large MLC performed adequately across different PTV sizes, the CL value of RD GPR at 2%/1 mm fell below 90%. This indicates that the contribution of PTV margin might be considered for a large MLC in SRS/SRT.

KEYWORDS stereotactic radiosurgery, stereotactic radiotherapy, multi-leaf collimator, dosimetric parameter, gamma analysis

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INTRODUCTION

Radiosurgery is a specialized radiotherapy technique commonly employed as an alternative approach for treating intra-cranial lesions. This

treatment technique is mostly employed in intra-cranial abnormalities, e.g., the vascular malformations, brain tumors and brain cancer, when the primary treatment method (surgical intervention)

is not feasible. Two treatment techniques are encompassed in this treatment approach: stereotactic radiosurgery (SRS), which involves delivering a single large radiation dose to the target (1), and stereotactic radiation therapy (SRT) which administers a high radiation dose over multiple fractions. Due to the high radiation dose of the treatment, the size and volume of the target lesion are limited (range 1-35 cm³) (2) to prevent complications from radiation that can occur in nearby normal tissue. The American Association of Physicists in Medicine no. 54 (3) (AAPM no. 54) released a guideline on this treatment technique which emphasized not only the accuracy of delineation but also the rapid falloff of the outside radiation dose. Delineation accuracy was improved by utilizing image registration among multiple modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Various other treatment modalities have been employed in this technique, including Gamma Knife® (4), C-arm based linear accelerator (5, 6) C-arm linac, tomotherapy (7-9) and CyberKnife® (10).

AAPM no. 54 is not limited to specific treatment modalities. A C-arm Linac is widely used as a radiosurgery technique. This machine can benefit from being equipped with various aperture devices for SRS/SRT (2, 11-13) such as cylindrical collimators (CC), mini multi-leaf collimators (mMLC), multi-leaf collimators (MLC), etc. Currently, the use of mMLC and MLC is widespread because the shape variation of the machine aperture. This provides advantages in the performance of the treatment technique in photon fluence modulation, e.g., intensity modulation radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). These sophisticated techniques can control the conformity of the radiation volume on the target and can also provide a high dose gradient outside the target as well. However, the width of the MLC may impact the delivered dose distribution to the lesion, particularly a small target. Larger MLCs have a wider leaf, which can reduce precision in shaping the radiation beam to the target contours which can lead to a less conformal dose distribution. Additionally, larger MLCs create a wider penumbra, the region at the edge of the radiation field where the dose rapidly falls off. This penumbra can result in less high dose gradients, reducing the precision

of dose confinement to the target and potentially increasing the dose to surrounding healthy tissues. The recommendation for mMLC of less than 5 mm leaf width might be beneficial for a small target volume (12). Although the use of mMLC is suitable for a radiosurgery, its use might be limited in a clinical practice, e.g., the treatment of a large target. The performance of large MLCs (5 mm leaf width) has been compared to a mMLC (14-20). Although a small MLC provided better dosimetric parameters (15, 16) than a large MLC such as the conformity index (CI) and gradient index (GI), no significant difference was found between these two sizes of MLC (14, 17-20).

CI is the most significant dosimetric parameter in the plan quality of radiosurgery. Many publications (14, 17-20) have found no significant differences in this parameter among different MLCs. Utilizing a large MLC, a decreasing value of CI according to The International Commission on Radiation Units and Measurement (CI_{ICRU}) (21) or an increasing value of CI according to Paddick (CI_{Paddick}) (22) is observed when the volume of the target is increased (19, 23). This evidence may not only impact the plan qualities (16, 20, 24) but also the delivered dose in a treatment. With a large width MLC, achieving a high CI becomes challenging, which means the radiation dose is less well confined to a small target volume. This can compromise the effectiveness of the treatment and increase the risk of side effects. The use of large MLCs also requires experimental dosimetric procedures using Patient Specific Quality Assurance (PSQA) including protocols for verifying that the delivered dose distribution matches the planned dose distribution as measured by gamma analysis. The objective is to assess the feasibility of using large MLCs in intra-cranial single lesion stereotactic radiosurgery techniques by evaluating dosimetric quality parameters and conducting gamma analysis.

METHODS

Patient Selection and Treatment Planning

This retrospective study recruited patients with a single brain lesion between January 2019 and December 2023. The sample size of 69 patients was calculated using the Danial formula (25). The sample included 41 males and 28 females with a median age at 45 years (range 9-76 years).

All selected patients underwent a CT Simulator (SOMATOM Definition AS, Siemens Healthineers, Forchheim, Germany) with a slice thickness of 1 mm. Patients were immobilized using a specific thermoplastic mask for SRS/SRT techniques. The CT images set was registered with MRI images with T1-weighted for a delineation (target and normal structures). The Planning Target Volume (PTV) was expanded by 1-2 mm from the Gross Target Volume (GTV). In this group of patients, 23 cases were treated with the SRS, and 46 cases underwent the SRT. The treatment plans were created by the MONACO® treatment planning system (TPS) version 6.1.3.0 (Elekta, Stockholm, Sweden) using the Monte Carlo Algorithm Calculation. All treatment plans calculated the dose using a grid size of 1-2 mm. The geometrical radiation beam included 3-5 non-coplanar arcs with the VMAT technique using 6 MV photons. The MLC of the C-arm Linac (Synergy®, Elekta, Stockholm, Sweden) was upgraded by replacement with a 5 mm MLC leaf width. Before delivery, the position was verified by using a cone beam

CT system and was corrected by the 6 degrees of freedom couch. This study was approved by Ethics Committee of Chiang Mai University on 19 Nov 2023 (study code: RAD-2566-055).

PSQA preparation and Gamma analysis

PSQA was conducted using the SRS MapCHECK® (SRSMC) (Sun Nuclear Co., Melbourne, FL, USA). This device has been used in clinical practice since September 2023. The SRSMC consists of an inserted 2D diode array in a Sun Nuclear StereoPHAN®, a polymethyl methacrylate (PMMA) material with a cylindrical shape and one round end (SRS phantom system) (Figure 1A). The beam geometries of the treatment plan were transferred onto this phantom system. Although the non-coplanar technique is employed in clinical practice, this study designed the beam geometries with zero degrees of couch and gantry angle arrangement as illustrated in Figures 1B and 1C. The PSQA plan dose distribution was then recalculated using a 1 mm resolution and exported to SNC Patient software version 8.5 (Sun Nuclear

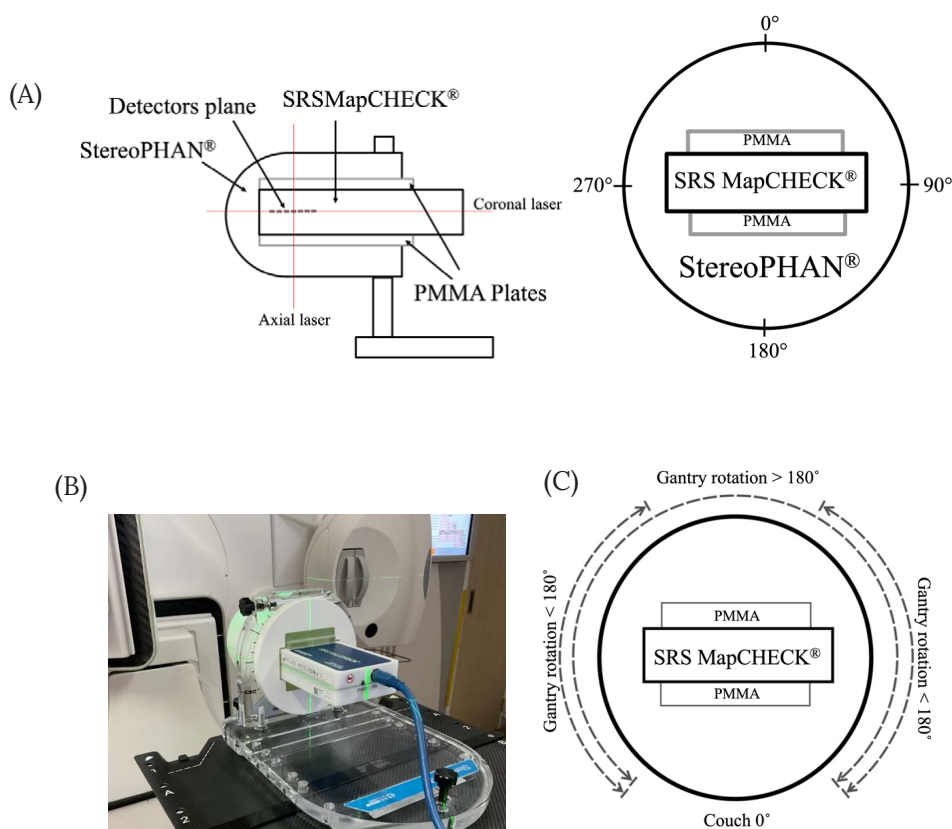


Figure 1. Diagram and phantom setup position. (A) SRS phantom diagrams, (B) SRS phantom setup, (C) Gantry angles arrangement in the PSQA treatment planning

Co., Melbourne, FL). For the dose measurement, a surface guided radiation therapy (SGRT) system (Catalyst HD® system, C-RAD®, Uppsala, Sweden) was employed to ensure the delivery set-up position. The PSQA measurement method utilized a true composite at zero degrees of couch.

Dosimetric parameters and evaluation tools

Various dosimetric parameters were utilized to assess the feasibility of a large MLC in SRS/SRT including the CI_{ICRU} (21), $CI_{Paddick}$ (22), GI (26), modulation factor (MF) (27), and the fluence map variations (FMV). The FMV was calculated using the standard deviation (SD) provided by the TPS. This system reported a photon fluence of leaf template summation per arc gantry as illustrated in Figure 2. The SD of the fluence can represent the plan complexity without having an impact on the scatters in the monitor unit calculation. The formulas and ideal values of these dosimetric parameters are described in Table 1. To evaluate the Gamma analysis, the results of PSQA plans across various PTV sizes were analyzed using the Gamma criteria (28) at 2%/2 mm and 2%/1 mm, with a 10% low dose threshold. The Gamma passing rate

(GPR) was calculated both with an absolute dose (AD) and with a relative dose (RD). The standard guideline recommends this value should not be below 95% for a complex treatment plan (29).

Confidence limits (CL)

The confidence limits value represents the plan quality assurance in each center and was determined by the formula of the AAPM TG119 recommendation as shown in Table 1. The formula is expressed as $(100 - \text{mean}) + 1.96\sigma$, where the mean is the average value of the GPR and σ is the SD of that value. A value might increase or decrease depending on various factors such as the implementation of new treatment techniques and measuring devices, new staff orientation, etc. Although there were no recommended passing criteria of CL, our center agreed that the CL value should not be below 90%. The performance of the large MLC in SRS/SRT was also accessed using this parameter as well.

Statistical analysis

Significant correlations were investigated among different sizes of PTV, dosimetric indexes,

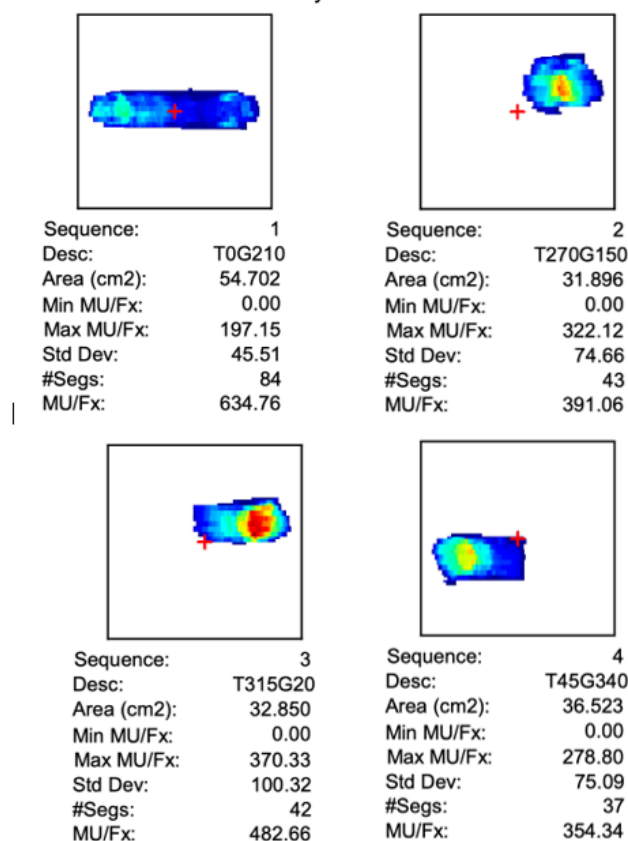


Figure 2. Characteristics of photon fluence in each gantry arc per treatment plan where sequence is the number of gantry arc

Table 1. Mathematical definition of dosimetric parameters

Dosimetric index	Definition	Ideal value	References
Conformity index			
ICRU	$CI_{ICRU} = PIV / PTV$	1	ICRU (21)
Paddick	$CI_{Paddick} = TV_{PIV}^2 / (PTV \times PIV)$	1	Paddick (22)
Gradient index	$GI = PIV_{50\%} / PIV_{100\%}$	As low as possible	Paddick and Lippitz (26)
Modulation factor	$MF = MU / Dose$	-	Chiavassa et al. (27)
Fluence map variation	$FMV = \sigma_{\text{photon fluence}} / \text{dose}$	-	-
Confidence limits	$CL = (100 - \text{mean}) + 1.96\sigma$	*Remark	AAPM TG-119 (30)

*Remark: should be as much as possible or depend on the individual treatment center agreement.

CI_{ICRU} , conformity index of ICRU; PIV, prescribed isodose volume; PTV, planning target volume; $CI_{Paddick}$, conformity index of paddick; TV_{PIV} , treated volume of PIV; GI, gradient index, $PIV_{50\%}$, volume of 50% isodose level of the prescribed dose; $PIV_{100\%}$, volume of prescribed dose; MF, modulation factor; MU, monitor unit; FMV, fluence map variation; σ , standard deviation; CL, confidence limits.

Table 2. Mean value±standard deviation of various sizes of PTV, dosimetric parameters, and treatment plan complexity

Range of PTV (cm ³)	Number of cases	PTV (cm ³)	CI_{ICRU}	$CI_{Paddick}$	GI	MF	FMV
$x \leq 5.0$	32	2.16±1.27	1.40±0.19	0.71±0.10	6.94±2.07	3.09±0.64	0.09±0.03
$5.0 < x \leq 10.0$	14	6.59±0.98	1.23±0.06	0.81±0.04	4.36±0.47	3.26±0.62	0.09±0.02
$10.0 < x \leq 15.0$	7	12.55±1.40	1.17±0.07	0.87±0.02	3.49±0.43	3.91±0.77	0.12±0.01
$15.0 < x \leq 20.0$	7	17.20±1.29	1.15±0.04	0.85±0.05	3.30±0.18	3.43±0.82	0.11±0.03
$20.0 < x$	9	25.56±3.31	1.19±0.09	0.83±0.07	3.44±0.71	4.15±1.37	0.12±0.05
Total	69	8.69±8.38	1.29±0.17*	0.77±0.10*	5.24±2.18*	3.38±0.87*	0.10±0.03*
			($p < 0.001$)	($p < 0.001$)	($p < 0.001$)	($p = 0.002$)	($p < 0.001$)

*Significant correlation between PTV sizes and parameter

PTV, planning target volume (x); CI_{ICRU} , conformity index of ICRU; $CI_{Paddick}$, conformity index of paddick; GI, gradient index; MF, modulation factor; FMV, fluence map variations

plan complexity and GPRs. Statistical significance was analyzed using Spearman's correlation with a confidence interval of 95% ($p < 0.05$) indicating statistical significance. The analysis was conducted using SPSS version 29.0.2.0 (IBM Co., Armonk, New York, USA).

RESULTS

Correlations among PTV, CI, GI and treatment plan complexity

This study involved different sizes of PTV ranging from 0.34 to 30.42 cm³ with a mean volume of 8.69±8.38 cm³ (mean±SD). The size of PTV was classified into 5 groups as illustrated in Table 2. The smallest size (volume < 5 cm³) was 46.38% while for the 5-10 cm³ size it was 20.28% of a total number of samples. The size that had a volume larger than 10 cm³ was 33.34%. Table 2 demonstrates not only the characteristics of PTV but also other parameters and indices. The values of CI were 1.29±0.17 and 0.77±0.10 for the ICRU and Paddick, respectively. These results showed

a moderately significant correlation ($p < 0.001$) between the PTV sizes versus CI_{ICRU} ($r = -0.676$) and the PTV sizes versus $CI_{Paddick}$ ($r = 0.670$). The mean GI had a value of 5.24±2.18, and a significant negative correlation ($r = -0.913$, $p < 0.001$) with PTV size. The complexity values of the treatment plan were 3.38±0.87 and 0.10±0.03 for the MF and the FMV, respectively. There was a low but statistically significant correlation between the PTV sizes and MF ($r = 0.363$, $p = 0.002$) and between PTV sizes and FMV ($r = 0.444$, $p < 0.001$).

Gamma passing rate and its correlation

This study employed the SRSMC to measure the GPR. Table 3 shows that the criterion at 2%/2mm had values of 92.42±3.74 and 96.38±3.24 for AD and RD GPR, respectively. The study also observed a tightened distance-to-agreement (DTA) with the criterion set at 2%/1 mm. This criterion had values of 82.03±6.69 and 89.64±7.26 for the AD and RD GPR, respectively. Significant correlations were observed for the following: $r =$

Table 3. Mean value $\pm$ standard deviation of various sizes of PTV, gamma passing rate, and confidence limits

Range of PTV (cm ³)	Number of cases	PTV (cm ³)	GPR 2%/2mm (%)		GPR 2%/1 mm (%)	
			AD	RD	AD	RD
$x \leq 5.0$	32	2.16 $\pm$ 1.27	93.32 $\pm$ 3.03	97.06 $\pm$ 2.93	82.60 $\pm$ 6.10	91.47 $\pm$ 5.89
5.0 < $x \leq 10.0$	14	6.59 $\pm$ 0.98	91.11 $\pm$ 2.81	96.45 $\pm$ 2.53	79.56 $\pm$ 6.06	89.78 $\pm$ 5.62
10.0 < $x \leq 15.0$	7	12.55 $\pm$ 1.40	91.83 $\pm$ 5.06	94.73 $\pm$ 4.40	81.29 $\pm$ 7.34	85.54 $\pm$ 10.33
15.0 < $x \leq 20.0$	7	17.20 $\pm$ 1.29	92.20 $\pm$ 4.11	94.80 $\pm$ 3.81	83.31 $\pm$ 7.23	84.97 $\pm$ 10.29
20.0 < x	9	25.56 $\pm$ 3.31	91.93 $\pm$ 5.66	96.33 $\pm$ 3.73	83.57 $\pm$ 8.87	89.73 $\pm$ 7.43
Total	69	8.69 $\pm$ 8.38	92.42 $\pm$ 3.74*	96.38 $\pm$ 3.24	82.03 $\pm$ 6.69	89.64 $\pm$ 7.26*
			($p = 0.011$)	($p = 0.752$)	($p = 0.086$)	($p = 0.034$)
Confidence limits			85.09	90.03	68.92	75.41

*Significant correlation between PTV sizes and parameter

PTV, planning target volume (x); GPR, gamma passing rate; AD, absolute dose; RD, relative dose

-0.304 ($p = 0.011$) for PTV size versus AD GPR at 2%/2 mm, and $r = -0.256$ ($p = 0.034$) for PTV size versus RD GPR at 2%/1 mm. No significant correlations were found between PTV size and RD GPR at 2%/2 mm or AD GPR at 2%/1 mm. No significant correlations were found between GPR and GPR and complexity or between either MF, FMV and GPR.

Confidence limit (CL)

The CL was calculated based on overall GPR (Table 3). With a large MLC in the SRS/SRT, the CL revealed a value of 85.09% and 90.03% for the AD and RD GPR, respectively, using the criteria of 2%/2 mm. With tightened DTA, the results revealed values of 68.92% and 75.41% for the AD and RD GPR, respectively.

DISCUSSION

This study investigated the feasibility of using a 5 mm MLC leaf width in SRS/SRT for various PTV sizes by analyzing dosimetric parameters, plan complexities and GPRs.

Correlations among planning target volume, conformity index, gradient index, and treatment plan complexity

In terms of dosimetric parameters, the dose coverage of the target by CI assesses whether the prescribed dose conforms to the shape and size of the target volume. To observe the impact of CI and PTV sizes, these two parameters were plotted as illustrated in Figure 3. The trend line, a power function, reveals that both CI_{ICRU} and CI_{Paddick} were improved when the PTV sizes were increasing. These results confirm the work of

Dhabaan et al. (31) and Li et al. (32) Obviously, a large width of MLC might limit the ability to achieve optimal dose conformity, particularly for a small PTV. With a large width, it can be difficult to modulate the intensity precisely around a small target, resulting in less conformal dose coverage on the target. This impact was observed not only in this study but also in the work of Li et al. (13), Jalbout et al. (33) and Watcharawipha et al. (9,34)

Additionally, the GI is an important factor that represents the dose falloff in the surrounding normal tissue of the SRS/SRT. A low value of GI indicates not only a steep dose falloff outside the target but also good sparing of surrounding tissue. Figure 4 shows a steep dose gradient that was improved (decreasing GI value) as the PTV sizes were increased. This result aligns with previous studies by Ohtakara et al. (35) and Popple et al. (36) A large width of MLCs might produce broader penumbra regions, leading to less steep doses in a small lesion. That limitation could be more pronounced where precise dose distribution is critical. This observation confirms the work of Menon et al. (37) and Desai et al. (38)

The complexity of a radiation treatment plan was defined by the MF which is the ratio between the MU and the fraction dose. An increase in MU in the same beam geometry can indicate the complexity level of each plan, i.e., a high MF value indicates a high treatment planning complexity. Figure 5A shows the treatment plan complexity in terms of MF, which escalates with an increase in the PTV size. This result is consistent with the study of Li et al. (39) Additionally, the present study introduced an in-house evaluation tool, the FMV. The limitation of the MF may be due to MU

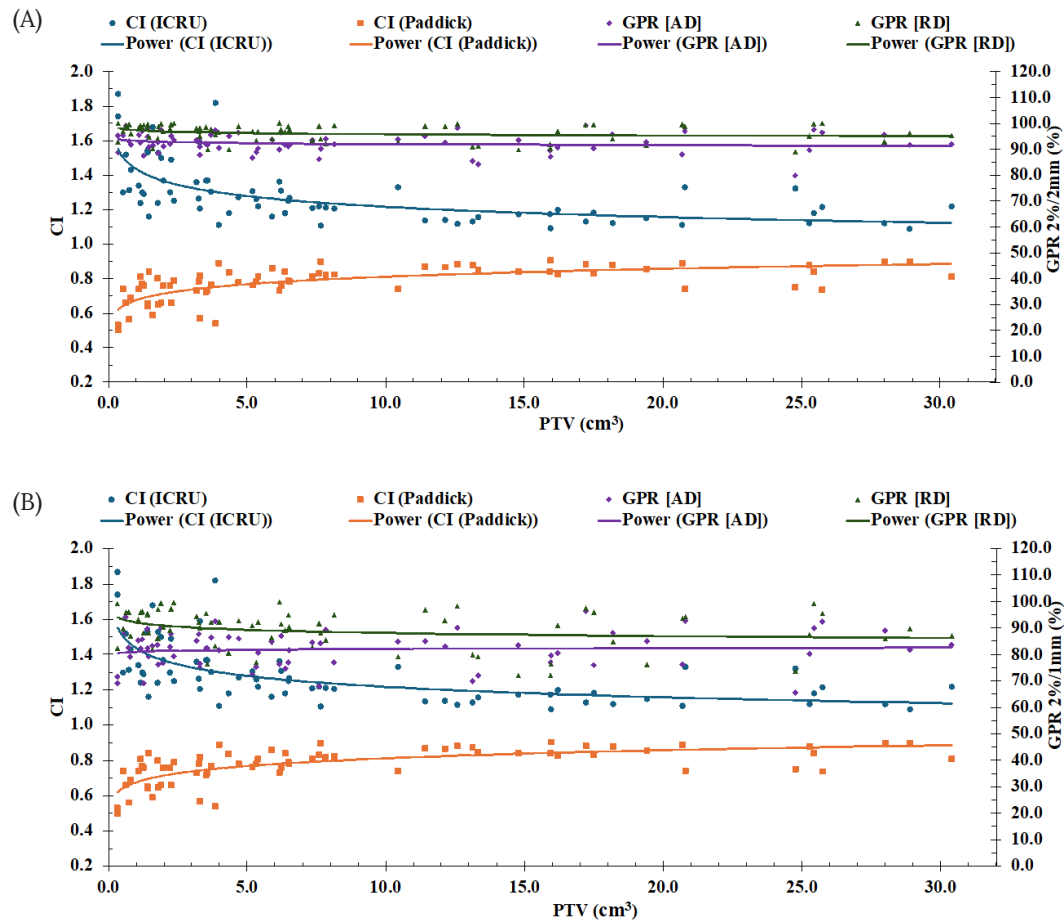


Figure 3. Plots and trend lines among various planning target volume (PTV) sizes, conformity index (CI), gamma passing rate (GPR): GPR 2%/2mm (A) and GPR 2%/1mm (B).

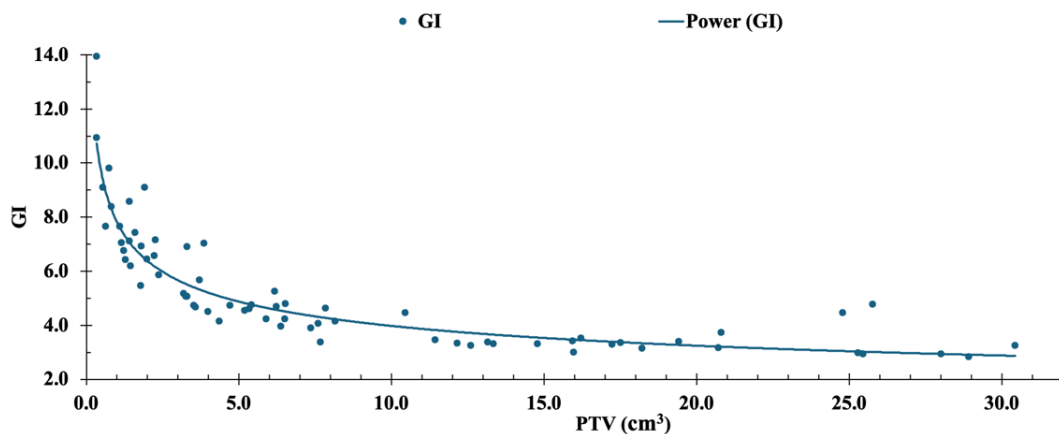


Figure 4. Plots and trend lines with various planning target volume sizes and gradient index

calculation in a small field size. This value may increase due to a lack of photon scatter in a small field size, even if the photon fluence was equal to a larger field size. The FMV may more accurately represent plan complexity than the MF due to variations in photon fluence. Figure 5B clearly demonstrates the high complexity of the treat-

ment plan in terms of FMV for a large PTV.

Gamma passing rate and its correlation

In the PSQA, the beam geometries were designed with a zero-degree couch angle in this study. These geometries aimed to eliminate phantom position uncertainty caused by couch

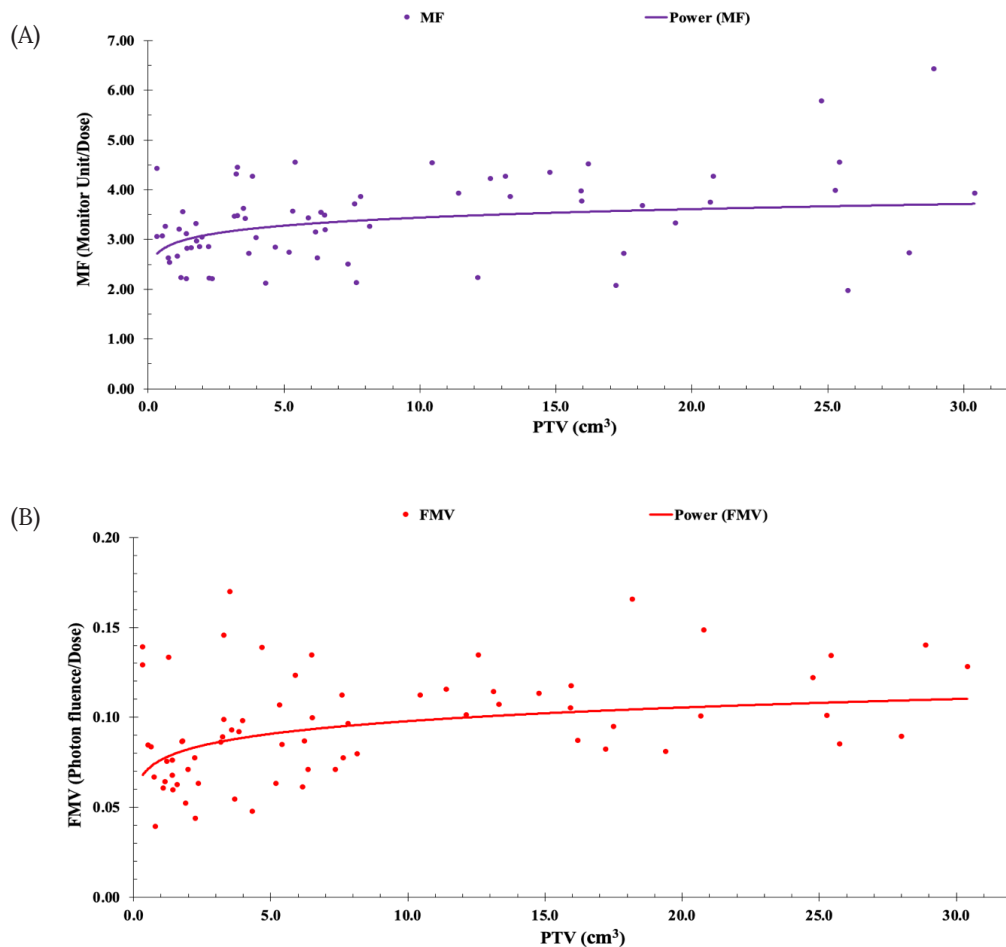


Figure 5. Plots and trend lines with various planning target volume (PTV) sizes, modulation factor (A) and fluence map (FM) variations (B).

rotation. Although the value of GPR differed between couch rotation and no couch rotation, no significant difference was found in either the AD ($p = 0.313$) or RD ($p = 0.429$).

In this study, the GPR value of 2%/2 mm was more than 90% higher than the GPR at 2%/1 mm. The GPR value decreased when tighter criteria were applied. Although the margin of PTV was calculated based on the uncertainty of the patient setup, this error could be reduced by image guided radiation therapy (IGRT) or SGRT. This clearly shows that the impact on the PTV margin remained. The margin could thus be attributed to 2 mm, particularly the impact of a large MLC in SRS/SRT. The correlation was observed between plan complexity and not only the AD GPR but also the RD GPR. Due to the variation in output of the Linac, the RD GPR closely represented the shape of the treatment planning dose distribution. In this study, the AD provided a lower value than the RD which indicates that the machine output

impacted the GPR evaluation. This can be clearly observed in the AD GPR at 2%/1mm. The AD measurement showed a lower value while the RD value was similar to the other PTV groups. Figure 6 shows the GPR increasing simultaneously with decreasing plan complexity. This result confirms the work of Chiavassa et al. (27)

The dose distribution in terms of dosimetric plan quality was assessed. The results showed that the CI and GI impacted a small PTV size but improved for a larger PTV size. However, in terms of the PSQA, a large MLC was able to shape the beam precisely for a small PTV size. This is shown in Figure 3, which illustrates a slight impact on the GPR value with increasing PTV size. It also demonstrates that a large MLC enhances the precision of delivery of planned dose distributions. The VMAT was the technique that delivered a small beamlet to the target. Ability to limit the size of each beamlet depended on the treatment machine. Accuracy of MLC positions could

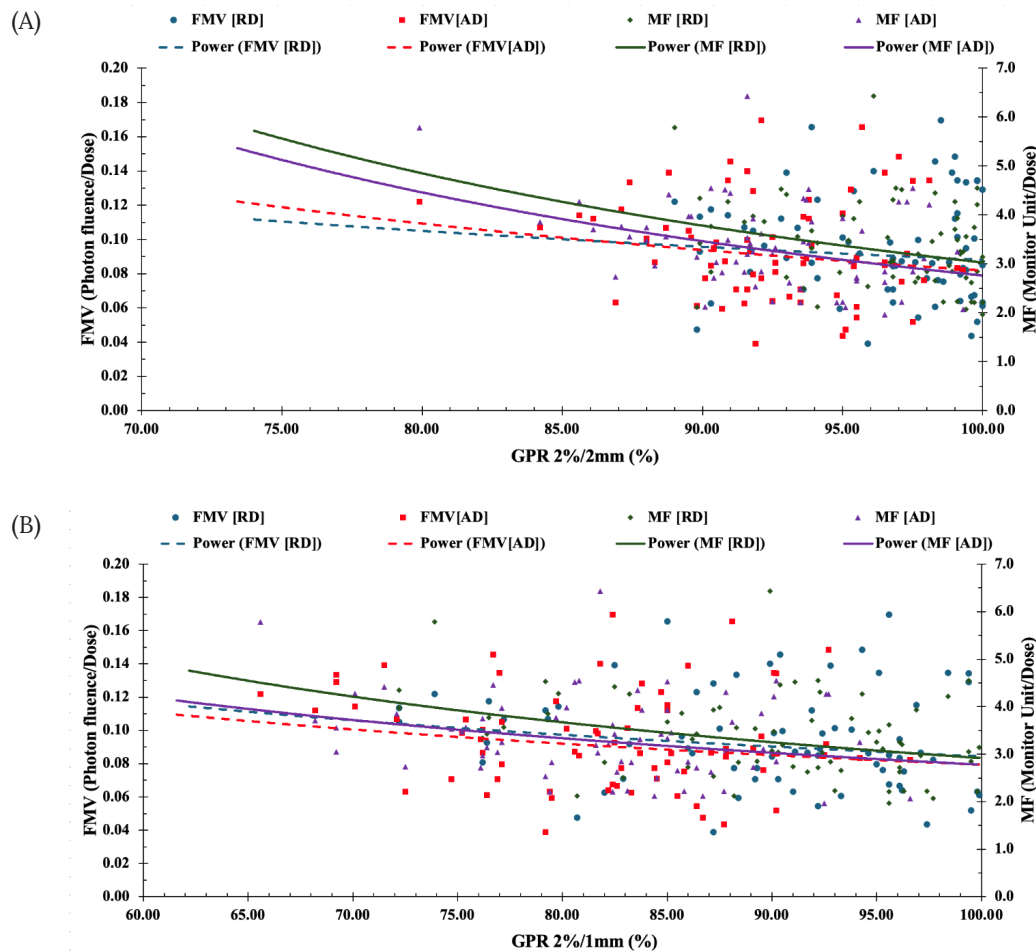


Figure 6. Plots and trend lines among various gamma passing rates (GPR), fluences map variations (FMV) and modulation factor (MF). GPR 2%/2mm (A) and GPR 2%/1mm (B)

be achieved, but at the cost of a trade-off in the CI value, particularly in the case of a small target. Statistical analysis found no significant correlations between plan complexity and GPR. The PTV size did not impact the GPR value, although increasing the size led to greater plan complexity. This demonstrates that a large MLC is effective in terms of increasing treatment plan complexity.

Confidence limit

The CL was used to ensure the level of treatment planning accuracy. Although there was a recommended GPR level (29), the level of CL had to be determined for each center. This study illustrates that a large MLC might cause a large SD in the GPR. These results demonstrated a low CL value when compared to studies with a small MLC in this treatment technique (40, 41). The variation in radiation output is one factor that can cause a wider range of SD values, particularly the AD. Therefore, the AD may not be suitable for CL estimation compared to RD (29). Although there

was a guideline on the tolerance limit value of the GPR, it was not on the CL. Our center then setup a tolerance limit for the CL that it should not be below 90% for the RD GPR at 2%/2 mm.

This study aimed to investigate the feasibility of using a large MLC in SRS/SRT. The investigation found the considerations of utilization in terms of the CI, GI, MF, FMV and GPR, that were against the PTV size. The results found a significant correlation between PTV size and all dosimetric parameters with the exception of RD GPR at 2%/2mm and AD GPR at 2%/1mm. This might be an issue when employing MLC in a small lesion as it would decrease the plan qualities of the CI and GI. Although plan complexity was significantly correlated with the PTV size, the MLC was able to achieve a satisfactory performance as indicated by the value of GPR. However, the GPR is one factor to consider when applying the 2%/1 mm criterion. The setup margin should be taken into account when using this size of MLC. Multiple lesions, however, present an interesting area for future research.

CONCLUSIONS

This study investigated the feasibility of a large MLC with various PTV sizes for a single lesion in the SRS/SRT. The study identified factors that should be considered when utilizing this size of MLC. The plan qualities of the CI and GI decreased when a large MLC was applied in a small lesion. Although this size of MLC can achieve a satisfactory performance with various PTV sizes, the CL value of RD GPR at 2%/1mm was found to be below 90%. Another consideration is that the setup margin could be contributing 2 mm in the PTV.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author contributions

A.C.: Conceptualization, data curation, investigation, formal analysis, writing—original draft, writing—review and editing; A.W.: conceptualization, formal analysis, writing—review and editing, Supervision; W.N.: formal analysis, writing—review and editing; A.K., B.J.: formal analysis.

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