RESEARCH ARTICLE

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Comparison Flattening Filter and Flattening Filter-Free Techniques in Small-Fields Dosimetry with Various Types of Detectors

Elsayed M. Alashkar^{1*}, Hussein M. Abdelhafez¹, Mahmoud A. Kenawy^{1,2}, Gamal M. Hassan³, Khairy T. Ereiba¹, Abdullah Megahed⁴

Abstract

Purpose: The aim of this study was to investigate the detector size effect on small-field dosimetry and compare the performance of 6MV WFF/FFF techniques. Methods: We investigated the detector size effect on small-field dosimetry and compared the performance of 6MV WFF/FFF techniques. PDD, profile curves, and absorbed dose were measured in water under reference conditions with 6MV (WFF/FFF) techniques. We employed Farmer FC65-P, CC13, CC01, and IBA Razor diode, with Versa Lineac. Subsequently, we replicated this assessment for small-fields under 5cmx5cm dimensions. **Results:** For both 6MV WFF/FFF, significant dose differences (Dmax=1.47cm), were ±4.55%, $\pm 6.7, \pm 12.75\%$ and $\pm 33.3\%$ for 4cmx4cm, 3cmx3cm, 2cmx2cm, and 1cmx1cm, respectively. The average difference relative to D10 was observed to be $\pm 4.66\%$, $\pm 5.73\%$, $\pm 6.58\%$, and $\pm 8.75\%$ for the previous field sizes. Differences between WFF/FFF are neglected values at all field sizes>2.3%, also, the output of the largest detector FC65-P is lower at 55% in the smallest field size. Variation in the profile doesn't exceed a difference of >5% in flatness between WFF/ FFF at depth10cm, across all fields, while symmetry is >1%, but radiation output is considerably lower at 55% for FC65-P chamber in 2cmx2cm, 1cmx1cm compared to the CC01 chamber and Razor diode. Significant differences in 1cmx1cm, where FC65-P chamber exhibits around 49% difference compared to Razor diode with 6MV (WFF/FFF). **Conclusions:** Significant differences were observed in doses with various detectors. Detector-size influences the dose. WFF/FFF techniques show no major differences in small-fields dosimetry. Utilize some situations the advantage of FFF boasting a higher dose rate, consequently reducing treatment time to half.

Keywords: Absolute Dose- small field dosimetry- flattening filter-free beam- ionization chamber- razor diode

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Introduction

In external radiation therapy, high-energy beams are directed toward the target using conventional linear accelerators to achieve uniform intensity across the treatment field flattening filter (FF) was commonly employed. But at the beginning of the 19th century, an increasing interest focused on the usage of Flattening filter-free (FFF) clinical practice due to its widespread application in advanced radiotherapy treatment techniques where homogeneous dose delivery is not necessary [1, 2]. An immense number of studies reveal that the removal of FF (Flattening Filter/flattened beam) becomes highly beneficial due to the occurrence of potentially desirable properties such as increased dose rate, reduced treatment time, reduced out-of-field dose, reduced surface dose, reduced head scatter, and reduced organ movement error [3]. Furthermore, the removal of FF would even reduce the risk of secondary cancer encounters in Intensity-Modulated Radiation Therapy (IMRT) and/or Volumetric Modulated Arc Therapy (VMAT) [4-6]. These techniques, especially in Stereotactic Radiosurgery (SRS), O'Brien et al. [1], and Stereotactic Body Radiation Therapy (SBRT), prioritize higher doses in the center of small tumors and reduced doses in the periphery [7, 8]. Since we need the doses in the center and be nearly flat over the central few centimeters, which is achieved with radiotherapy without the flattening filter [9]. Furthermore, FFF fields may be useful for small or moderate targets [10]. Some studies have found that the FFF technique produces a more uniform dose distribution and reduces the dose perturbation effect in small fields, while others have found that the MV WFF is still necessary to achieve accurate dose delivery. Acutely, the advantage of the MV FFF

¹Physics Department, Faculty of Science, Al-Azhar University, Cairo, Egypt. ²Radiology Techniques Department, College of Health and Medical Techniques, Al-Mustaqbal University, Iraq. ³Ionizing Radiation Metrology Laboratory, National Institute of Standards (NIS), Giza, Egypt. ⁴DepartmentofRadiotherapy, Shefaa-Alorman Hospital, Egypt. *For Correspondence: ph.alashkar@azhar.edu.eg

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technique is that it can deliver higher dose rates, which can reduce treatment times and improve patient throughput.

FFF technology has been in clinical use for many years, starting with the Scanditronix racetrack microtron MM50 [11]. However further research is needed to fully understand the advantages and limitations of each technique in different clinical scenarios because the radiation behavior in small fields is still challenging in research, whether using FF or FFF. In small-field dosimetry, the use of a WFF and FFF in the linear accelerator can lead to significant dose perturbations, which can affect the accuracy of the delivered dose. These and other dosimetry protocols are based on measurements using an ionization chamber of absorbed dose to water, traceable to a primary standards dosimetry laboratory (PSDL) [12], at reference conditions, such as a conventional field size of 10cmx10cm, ConventionalCodes of Practice (COPs) such as Technical Reports Series (TRS-398) [13], the American Association of Physicists in Medicine (AAPM) publication titled AAPM's TG-51 Protocol [14]. Choosing the right detector for measuring radiation dose in small fields can be a challenging undertaking, and it's essential to opt for a detector that operates at a sensitivity enough for radiation dosimetry [15]. There is no consensus among researchers on the use of specific types of detectors. For this reason, the International Atomic Energy Agency has conducted a study and developed a protocol for working in small fields and how to measure them, while setting some conditions to achieve accurate measurements TRS-483 Protocol on Small Field Dosimetry" [16, 17]. The radiation detector's dose linearity is based on TRS-483, identifying deviations at low doses and proposing a 1.0% tolerance due to non-linearity, Linearity confirms detectors meeting the 0.1% criterion using squared Pearson's correlation coefficient r2. Leakage results support detectors' suitability for small-field dosimetry according to TRS-483 guidance [18]. In conventional broad beams, it is derived from a ratio of detector readings due to the practical independence of perturbation correction factors on field size [19]. However, such independence is not present in small-field dosimetry; particularly for perturbation factors and an output factor of absolute dose-to-water measurements will in almost all cases require an output correction factor to the measured detector reading ratio relative to the machine-specific reference field (fmsr). The symbol for a field output factor in IAEA TRS-483 is clinic field (fclin); (fmsr) (Qclin); (Qmsr) and Report of AAPM TG 155 [16, 1]. Field output correction factor. A field output correction factor is a correction that considers the variations in a detector's response between a non-reference (clinical) field and a machine-specific reference field [20], so small-field output factors need to be determined for every combination of beam energy and filtration (WFF or FFF) and field size as the differences between them can be statistically significant (P<0.05) [21].

Instrumentations and method

The instrumentation used in this study encompassed a range of advanced equipment tailored for precise measurements and analysis within the field of radiation therapy. The Elekta Versa-HD linear accelerator served as a pivotal tool, enabling measurements in more distinct techniques of the photon beams.

Instrumentations

Elekta Versa-HD linear accelerator

it was used to measure in two techniques of photon beams; 6 MV WFF and 6 MV FFF with various types of detectors.

Detectors specifications

FC65-P, CC13, and CC01 ion chambers and IBA Razor diode were employed, and their specifications are presented in Table 1.

Phantom specifications

(Blue Phantom2): it is a three-dimensional (3D) Water Phantom System for complete LINAC Commissioning & QA, scanning (48x48x48 cm³)

Electrometer specifications

(Reference Class ElectrometerDose2): Dose2 is a High-Performance Dual-Channel Reference Class Electrometer for reference dose and dose rate measurements in radiation therapy.

Radiotherapy software (myQA Accept)

it is fully workflow-oriented advanced beam scanning, efficient with menu-guided workflows, and scan data integration in myQA accept.

Materials and Methods

We investigated the characteristics of PDD in small fields using various detectors, with sizes equal to or smaller than 4cmx4cm, and in both 6 MV WFF and 6 MV FFF. Additionally, we examined the flatness and symmetry of these small fields.Furthermore, we measured the absorbed dose within a water phantom under reference conditions. These conditions encompassed a field size of 10cmx10cm, an SSD of 100cm, and a water depth of 10cm, as illustrated in Figure 1. A delivery of 100 MU was administered using all detectors, utilizing energy settings of both 6 MV WFF and 6 MV FFF.We have made the correction factors for the Razor diode to energies of 6 MV WFF and 6 MV FFF at the small fields.

Formalism

The measurement of absorbed dose to water in reference condition

A new method has been suggested for the reference dosimetry of atypical and small fields. This method establishes a connection between the Codes of Practice (CoP) commonly used in traditional radiotherapy techniques. In accordance with this newly proposed technique, the entire dosimetry process is carried out in a small field matched with the standard 10cmx10cm reference field based on Alfonso et al. 2008.

The measurement of absorbed dose to water under reference condition:

$$\mathbf{D}_{\mathbf{w},\mathbf{Q}_{\mathrm{msr}}}^{f_{\mathrm{msr}}} = M_{\mathbf{w},\mathbf{Q}_{\mathrm{msr}}}^{f_{\mathrm{msr}}} \cdot \mathbf{N}_{\mathbf{D},\mathbf{W},\mathbf{Q}_{0}}^{f_{ref}} \cdot \mathbf{K}_{\mathbf{Q},\mathbf{Q}_{0}}^{f_{ref}} \cdot \mathbf{K}_{\mathbf{Q}_{\mathrm{msr}},\mathbf{Q}_{0}}^{f_{\mathrm{msr}},f_{\mathrm{ref}}} (1)$$

 $M_{w,Qmsr}^{fmsr}$ The absorbed dose to water was measured in reference field dosimetry (msr) using corrected values that accounted for various factors such as pressure, temperature, ion recombination, polarity effects, electrometer factor, and beam quality factor.

ND $_{W O0}^{fref}$ is the ionization chamber's calibration factor in relation to absorbed dose to water determined at the national standards laboratory using Co60 beams at the national standards laboratory, $K_{Q,Q0}^{fref}$ is beam quality correction factor, and $K_{QmsrQ0}^{fmsr, fref}$ is another correction factor that must be taken into account due to variations in field size, shape, phantom material, and beam quality from the reference condition, in addition to the following factors which are taken into consideration (K_{tn} , K_{nol} , $K_{ele'}$ and K_{c}).

The absorbed dose within a small field at f_{clin} may not be the same as that at f_{msr} , the reference field. As a result, a new output factor, denoted as Ω , has been proposed for small fields. The value of Ω is dependent on the size of the field.

$$D_{w,Q_{clin}}^{f_{clin}} = D_{w,Q_{msr}}^{f_{msr}} \Omega_{Q_{clin}Q_{msr}}^{f_{clin},f_{msr}}(2)$$
$$\Omega_{Q_{clin}Q_{msr}}^{f_{clin},f_{msr}} = \frac{D_{w,Q_{clin}}^{f_{clin}}}{D_{w,Q_{clin}}^{f_{msr}}}$$

$$\lim_{k \to \infty} Q_{msr} = \frac{\overline{D_{w,Qmsr}^{fmsr}}}{\overline{D_{w,Qmsr}^{fmsr}}}$$

$$\Omega_{\text{Qclin},\text{fmsr}}^{f_{\text{clin}},f_{\text{msr}}} = \frac{M_{Q_{clin}}^{f_{clin}}}{M_{Q_{\text{msr}}}^{f_{\text{msr}}}} \cdot K_{\text{Qclin},\text{Qmsr}}^{f_{\text{clin}},f_{\text{msr}}}(3)$$

When measuring output factors, the normalized reference field utilized is usually significantly larger than the small fields under examination. Correction factors are thus crucial in minimizing errors and are deemed a fundamental aspect of calibration, as stated by O'Brienet et al. [22]. Correction factors are necessary to obtain accurate measurements, and they can be calculated using the following equation:

Correction Factor =
$$\frac{\left(\frac{D_{ref}}{D_{diode}}\right)small}{\left(\frac{D_{ref}}{D_{diode}}\right)ref}$$
 (4)

Results

The study aims to investigate the behavior of PDD, beam profile, and absolute dose measurements in small fields using different detectors and compare energies 6 MV WFF and 6 MV FFF.

a- The results revealed that the maximum dose delivered at a depth of D_{max} was at 1.47cm for both 6 MV WFF and 6 MV FFF energies with significant differences in dose penetration at D_{max} , D_{10} , and D_{20} that were measured at various field sizes, as shown in Table 2 and Figure 2.a. Initially, at measured 4cmx4cm and 3cmx3cm when utilizing the WFF technique at D_{max}, the average difference measurement was 4.55%, for the FFF group the average difference was 3.26%. At D₁₀ the average difference was 4.98% for the WFF and 4.35% for

Table 1. Provides the Detectors Specifications, and a Comparison of Various Detectors Used to Measure Ionizing Radiation, Highlighting the Distinctions in Type and Size among Them.

Detector Type	Active volume (cm ³)	Diameter (cm)	Total active Length (cm)
IBA Farmer FC65-P Ion chamber	0.65	0.62	0.23
IBACC13 Ion chamber	0.13	0.6	0.58
IBACC01 Ion chamber	0.01	0.2	0.36
IBA Razor -diode	0.002	0.06	0.4

the FFF. At D_{20} the average difference is 4.75% for the WFF and 4.05% for the FFF. When we make the same previous comparisons with field 3cm x 3cm, we find that the average difference was 6.7% and 4.57% at D_{max} for WFF and FFF respectively, at D₁₀ the difference was 6.25% and 5.2% for WFF and FFF respectively and at D₂₀ was 5.83% for WFF and 4.93% for the FFF techniques.

In studying the measurement at 2cmx2cm and 1cmx1cm we found significant differences in dose penetration for doses at D_{max} , D_{10} , and D_{20} in comparison with conventional field size, as shown in Figure 2.b and Table 2, when utilizing the doses for the WFF technique at D_{max}, the average difference measurement was found to be 12.75%, about FFF group the average difference is 10.65%. At measuring at D_{10} the average difference is 7.05% for the WFF technique and 6.1% for the FFF technique. At measuring in D₂₀ the average difference is 6.1% for the WFF technique and 5.55% for the FFF technique.

When we make the same previous comparisons with field 1cmx1cm, we find that the average difference is 32.03% and 34.3% at D_{max} for WFF and FFF respectively, at D_{10} the difference is 8.78% and 8.73% for WFF and FFF respectively and at D₂₀ is 7.9% for WFF technique and 7.98% for FFF.

b- The maximum and minimum dose values on the 80% of the beam profile, the result manifests that the difference in the flatness of WFF and FFF beams at 10cm depth was found to be >5% with all field sizes and symmetry being>1%.

Lebel-Cormier et al. [23] examined the dose profile of a 2×2 cm² 6 MV beam was measured with a mean relative difference of 1.8% (excluding the penumbra region). The measured output factors for a 6 MV beam are in general agreement with the expected values within the experimental uncertainty. The detector response to different energies of photon and electron beams is within 5% of the mean response ($0.068 \pm 0.002 \text{ pm/Gy}$). The calorimeter's post-irradiation thermal decay is in agreement with the theory.

Figure 3 illustrates the radiation output is considerably lower at 55% for the FC65-P ion chamber in field sizes (2cmx2cm and 1cmx1cm), compared to the CC01 ion chamber and Razor diode in the same field sizes, also, the CC13 ion chamber lost 20% from charged particle equilibrium compared to the CC01 ion chamber and Razor diode at the measured beam profile at a distance of 1cmx1cm field size.

c- The absolute dose measurement under reference Asian Pacific Journal of Cancer Prevention, Vol 25 2107



Figure 1. The Detector Setup for the Determination of the Absorbed Dose in Water Phantom. The source-to-chamber distance is kept constant at 110 cm, field size 10 cm x 10 cm (reference) and measurements are made at depth 10 cm of water over the chamber.

conditions (SSD 100cm, D_{10} cm, and 100 Monitor Units (MU) being utilized) that measurements were taken at 6 MV FF and 6 MV FF at 1cmx1cm, 2cmx2cm, 3cmx3cm, and 4cmx4cm field size, we found the following: theinvestigation of various detectors for different narrow field sizes revealed at both energies 6 MV FF and 6 MV FFF, a significant discrepancy was found between all

detectors, for the 1cmx1cm field size, FC65-P exhibits a difference of approximately 49% compared to the readings from the Razor diode. The differences for the same field size are about 20.6% for CC13 and 6% for CC01. The average differences for all field sizes from 1cm to 4cm are 20.5%, 6.8%, and 1.7% for FC65-P, CC13, and CC01, respectively, as shown in Figure 4.



Figure 2. PDD Curves in a Water Phantom for a Field Size of 1 cm x 1 cm, 2 cm x 2 cm , 3 cm x 3 cm, and 4 cm x 4 cm; respectively; with an SSD of 100 cm, using 6 MV (WFF and FFF) with FC65-P, CC13 and CC01 ionization chambers and Razor diode detector.

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Energy	Detectors	Field size 4 cm x 4 cm			Field size 3 cm x 3 cm		
	Туре	PDD D _{max}	PDD at D ₁₀	PDD at D ₂₀	PDD D _{max}	PDD at D ₁₀	PDD at D ₂₀
6 MV WFF	FC65-P	95.70%	59.70%	34.70%	92.70%	57.00%	31.10%
	CC 13	96.90%	60.20%	33.00%	95.00%	58.00%	31.40%
	CC 01	94.80%	60.10%	32.90%	93.00%	57.40%	31.70%
	Razor diode	94.40%	62.10%	33.60%	92.50%	65.60%	32.50%
6 MV FFF	FC65-P	98.00%	62.20%	34.20%	95.50%	59.60%	32.60%
	CC 13	97.70%	61.70%	33.60%	96.00%	59.70%	32.30%
	CC 01	94.67%	63.30%	34.80%	95.20%	63.30%	27.10%
	Razor diode	96.60%	62.70%	34.80%	95.00%	61.30%	32.70%
Energy	Detectors	Field size 2 cm x 2 cm			Field size 1 cm x 1 cm		
	Туре	PDD D _{max}	PDD at D ₁₀	PDD at D ₂₀	PDD D _{max}	PDD at D ₁₀	PDD at D ₂₀
6 MV WFF	FC65-P	77.10%	48.70%	27.30%	37.60%	23.50%	13.10%
	CC 13	91.60%	54.80%	29.40%	73.30%	42.40%	22.10%
	CC 01	90.50%	54.50%	29.60%	80.80%	47.20%	24.70%
	Razor diode	89.80%	55.50%	28.40%	80.20%	45.10%	22.90%
6 MV FFF	FC65-P	79.10%	50.40%	28.40%	36.70%	23.10%	13.10%
	CC 13	92.70%	56.50%	30.40%	74.10%	43.40%	22.50%
	CC 01	93%	47.40%	25.70%	69.30%	39.90%	20.70%
	Razor diode	92.60%	53.50%	29.40%	82.40%	46.30%	23.30%

Comparison Flattening Filter and Flattening Filter-Free Techniques in Small-Fields Dosimetry with Various Types of Detectors Table 2. Measured PDD as shown D_{max} , D_{10} and D_{20} (cm) for Field Size of 4 cm x 4 cm, 3 cm x 3 cm, 2 cm x 2 cm and 1 cm x 1 cm of Energies 6 MV WFF and 6 MV FFF.

Also, when comparing the time taken for delivering 100 MU using the filtered 6 MV technique and the

filter-free 6 MV technique, we found that the average delivery time for 6 MV WFF was 10.14 seconds, while



Figure 3. Comparing the Beam Profile Curves for the Various Detectors; at a d10 cm in a water phantom, using (4 cm x 4 cm and 3 cm x 3 cm, 2 cm x 2 cm and 1 cm x 1 cm) field sizes with an SSD of 90 cm, and utilizing 6 MV WFF and 6 FFF techniques.



Figure 4. Measurements of the Variation of Relative Dose in a Small Field by the IBA Farmer FC 65-P, CC13, and CC01 (Ionization chamber) and Razor (diode) detector; with applied energies 6 MV WFF and 6 MV FFF.

for 6 MV FFF, it was 4.39 seconds.

The correction factor is calculated from this experiment for the Razor (diode) chamber by following Equation 4 is represented in Figure 5 for energies 6 MV (WFF and FFF). The correction factor measured from an experiment was found to be excellent and in agreement with the literature values for the small field, as shown in Figure 5.

Discussion

The study investigates the behavior of PDD, beam profile, and absolute dose within small radiation fields using various detectors by using 6 MV WFF and 6 MV FFF techniques to ensure the delivery of a precise and effective dose of radiation to a specific target and calculate

correction factors.

The results revealed that the maximum dose delivered at a depth of D_{max} was 1.47cm for both 6 MV WFF and 6 MV FFF energies. This value was found to be non-significantly different from the D_{max} depth obtained for the larger field size of 10cmx10cm which indicates that the distance for the maximum dose is not different from the conventional field size.

The results revealed that when measurements at D_{max} were taken in the small fields of 4cmx4cm, 3cmx3cm, 2cmx2cm, and 1cmx1cm, significant differences were found compared with the absorbed maximum dose at D_{max} , as follows: 4.55%, 6.7%, 12.75%, and 32.3%, respectively. These values pertain to the WFF technique, whereas the results for the FFF technique were 3.2%, 4.57%, 10.5%,



Figure 5. Correction Factor Curve for Razor (Diode) Detector; using IBA Farmer FC 65-P (ionization) chamber, applied energies 6 MV WFF and 6 MV FFF.

and 34.3%, respectively.

Also, at D_{10} taken in the same fields size significant differences were found compared with the conventional absorbed doses at D_{10} which equal 67.5%, as follows: 4.98%, 6.25%, 7%, and 8.78%, respectively. These values pertain to the WFF technique, whereas the results for the FFF technique were 4.3%, 5.2%, 6.1%, and 8.73%, respectively. At D_{20} taken in the same fields size significant differences were found compared with the conventional absorbed doses at D_{20} which equal 38.9%, as follows: 4.7%, 5.8%, 6.1%, and 7.9%, respectively. These values pertain to the WFF technique, whereas the results for the FFF technique were 4%, 4.9%, 5.6%, and 7.98%, respectively.

This signifies two things: firstly, the absorbed maximum dose at the maximum point, absorbed dose at staple depth D_{10} , and the decay region D_{20} were all affected by detector sizes, so there exists an inverse relationship between the size of the incident radiation beam and size of the measured detectors, the smaller the size of the detector, the decreases the fluctuations observed during measurements.

Secondly, there is no difference in discrepancies when utilizing both WFF and FFF techniques in small fields. The nominal beam profiles of both the WFF and FFF 6 MV photon beams for various field sizes of D_{10} at various detectors, which depicts that the lateral dose profiles with WFF differ non-significantly from the nominal flat profiles with the presence of FFF it is to be noted that the WFF and FFF beam profiles remain moderately similar for 4cmx4cm and 3cmx3cm. However, the significant difference in measurements of the detectors becomes evident in the 2cmx2cm and 1cmx1cm fields, where it becomes clear that detector FC65-P lacks the capability to accurately detect radiation more than other detectors.

The results obtained showed that the optimized beam energy and Full-width-half maximum value (FWHM) for small field dosimetry were affected by detector size. Since the results have shown that there is no significant variation in the beam profile within the horn region at shallow depths and marginal shoulders for small field depths, it can be inferred that the flatness of the beam profile remains relatively consistent for smaller field sizes in both WFF and FFF beams. As a result, these findings could offer potential benefits for various treatment techniques such as IMRT, SBRT, SRT, etc.

When validating absolute dose using various chambers, particularly with fields equal to or smaller than (4cmx4cm), a significant difference in LCPE (LINAC percent energy) has been observed. Notably, for the (1cmx1cm) field size, the FC65-P chamber shows a discrepancy of approximately 49% compared to the readings obtained from the Razor diode. Correspondingly, the differences for the same field size are approximately 20.6% for the CC13 chamber and 6% for the CC01 chamber. On average, across all field sizes ranging from 1cm to 4cm, the differences are 20.5%, 6.8%, and 1.7% for the FC65-P, CC13, and CC01 chambers, respectively.

These findings further reinforce that the measured readings with a specific detector depend on the detector's size. Additionally, there is no significant difference in using either the FF technique or the FFF technique. *Finally, when we compare the radiation behavior between* 6 MV WFF and 6 MV FFF

There was no significant difference in the radiation behavior delivered between 6 MV WFF and 6 MV FFF energies, except for the dose rate. The dose rate increased twofold in the 6 MV FFF, resulting in the dose rate doubling compared to the 6 MV WFF. The higher dose rate in 6 MV FFF led to a decrease in treatment time by approximately half or slightly more. For example, the average delivery time for 100 MU was 10.14 seconds for 6 MV WFF and 4.39 seconds for 6 MV FFF.

In conclusion, the study investigates the behavior of PDD, beam profiles, and absolute dose in small radiation fields using different detectors and 6 MV WFF/FFF techniques. The aim is to ensure accurate radiation dose delivery and calculate correction factors. The results suggest consistency in maximum dose at D_{max} for both techniques. Significant differences were observed in absorbed doses at various depths for small fields, with various detector sizes. Detector size influences the dose measurements, indicating an inverse relationship between the detected dose and detector size. On the other hand, both WFF and FFF techniques show no major differences in small fields' dosimetry. So, may utilize in some situations the advantage of FFF boasting a higher dose rate, consequently reducing the treatment time by approximately half.

Author Contribution Statement

All authors contributed equally in this study.

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Availability of data

Data is available upon request.

Ethical issue

Not applicable. No animal or human studies were carried out by the authors of this article.

Conflict of interest

The authors declare that they have no conflict of interest in this work.

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