

ORIGINAL ARTICLE

A treatment planning and delivery comparison of volumetric modulated arc therapy with or without flattening filter for gliomas, brain metastases, prostate, head/neck and early stage lung cancer

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ABSTRACT

Background. Flattening filter-free (FFF) beams are an emerging technology that has not yet been widely implemented as standard practice in radiotherapy centers. To facilitate the clinical implementation of FFF, we attempted to elucidate the difference in plan quality and treatment delivery time compared to flattening filter beams (i.e. standard, STD) for several patient groups. We hypothesize that the treatment plan quality is comparable while the treatment delivery time of volumetric modulated arc therapy (VMAT) is considerably shorter using FFF beams, especially for stereotactic treatments.

Methods. A total of 120 patients treated for head and neck (H&N) tumors, high-grade glioma, prostate cancer, early stage lung cancer and intra-cranial metastatic disease (both single and multiple metastases) were included in the study. For each cohort, 20 consecutive patients were selected. The plans were generated using STD- and FFF-VMAT for both 6 MV and 10 MV, and were compared with respect to plan quality, monitor units and delivery time using Wilcoxon signed rank tests.

Results. For H&N and high-grade gliomas, there was a significant difference in homogeneity index in favor for STD-VMAT ($p < 0.001$). For the stereotactic sites there were no differences in plan conformity. Stereotactic FFF-VMAT plans required significantly shorter delivery time compared to STD-VMAT plans ($p < 0.001$) for higher dose per fraction, on average 54.5% for 6 MV and 71.4% for 10 MV. FFF-VMAT generally required a higher number of MU/Gy ($p < 0.001$), on average 7.0% for 6 MV and 8.4% for 10 MV.

Conclusion. It was generally possible to produce FFF-VMAT plans with the same target dose coverage and doses to organs at risk as STD-VMAT plans. Target dose homogeneity tended to be somewhat inferior for FFF-VMAT for the larger targets investigated. For stereotactic radiotherapy, FFF-VMAT resulted in a considerable time gain while maintaining similar plan quality compared to STD beams.

Volumetric modulated arc therapy (VMAT) is a technique for delivering conformal dose distributions which consists of intensity-modulated radiotherapy (IMRT) delivered continuously as the gantry rotates around the patient in an arc [1]. During VMAT delivery the gantry rotation speed, multileaf collimator (MLC) field aperture and the dose rate are all simultaneously adjusted [2]. Comparisons between IMRT and VMAT have been reported in numerous studies confirming the potential of treatment time reduction and similar or better sparing of organs at risk (OARs) without compromising the dose to target [3–6].

Recently, the clinical use of flattening filter-free (FFF) beams and arcs have increased [7–9], following the clinical introduction of platforms with this functionality [10]. Removal of the flattening filter will result in a FFF beam with a conical shaped fluence distribution, an increase in dose rate and a reduction in head scatter that may result in shorter treatment times and beam-on times as well as a lower peripheral dose that may increase the possibility to spare OARs [11–13]. A reduction in treatment delivery time is favorable because of the increased risk of tumor displacement during a longer treatment

[14,15]. Flattened beams are being commonly used for practical and historical reasons but the ability of inverse planning that takes into account the beam profile during optimization facilitates the use of FFF beams [16].

A growing number of publications report on the potential benefits and disadvantages of FFF beams [17–21]. However, in contrast to our study, the majority of these publications have focused on a small cohort of patients with one diagnosis. A small cohort may limit the possibility of appreciate patient-to-patient variability as well as the possibility of performing a statistical analysis of the data.

The purpose of this study was to investigate the clinical applicability of FFF beams for several indications, and thus we might better judge where the technology could be of best use. Specifically, we investigated any difference in plan quality and treatment delivery time compared to our current standard of practice. We hypothesize that the treatment plan quality is comparable while the treatment delivery time required is considerably shorter using FFF beams, and that the benefit in treatment time would be the greatest for stereotactic, high dose per fraction treatments.

Material and methods

Patients and treatment sites

The patients in this study had all undergone treatment using STD-VMAT. A total of 120 patients (Table I) treated for high-grade glioma, WHO grade III–IV, bilateral head and neck (H&N) patients with oropharyngeal cancer with a gross tumor size of < 4 cm, early stage lung cancer with a tumor size of ≤ 6 cm, localized or locally advanced prostate cancer with a classification of T2–4 N0 M0 and intra-cranial metastatic disease regardless of primary tumor site using RapidArc® (RA) were chosen. The different treatment sites were selected to test a wide variety of tumor sizes, target and OAR geometries as well as dose constraints. For each cohort, 20 consecutive patients were selected, except for the intra-cranial metastatic disease patients where we selected 20 patients with a single metastasis [SRS (stereotactic radiosurgery) single metastasis] and 20 with multiple metastases (SRS multiple metastases). In this

work, we reserve the denomination of SRS for treatments with small field sizes (i.e. small tumor volumes) and high fraction doses. Treatment plans were generated using our current clinical protocol for each patient using FFF beams as well as conventional beams with flattening filter (denoted STD – standard) for both 6 MV and 10 MV generating a total of 480 VMAT plans.

Delineation and treatment planning

The different energies and their denotation were 6-MV flattened VMAT plan (STD6X), 6-MV FFF-VMAT plan (FFF6X), 10-MV flattened VMAT plan (STD10X) as well as 10-MV FFF-VMAT plan (FFF10X). For all plans, the dose calculations and optimizations were performed using the Eclipse treatment planning system version 11 (Varian Medical Systems, Palo Alto, CA, USA), anisotropic analytical algorithm (AAA) and progressive resolution optimization on 2 mm slice thickness computed tomography scans. All plans were designed to be delivered by a Varian TrueBeam™ STx linear accelerator. For the STD 6 MV and 10 MV plans, the maximal dose rate was set to 600 monitor units per minute (MU/min) while the FFF6X had it adjusted to 1400 MU/min and FFF10X to 2400 MU/min. This means that all plans used the maximum available dose rate for the corresponding technique and energy. All beam qualities were calibrated to deliver 1 Gy at dose maximum for a 10×10 cm² field at 100 cm SSD for 100 MU. It should be noted that 10 MV beams, to some extent, can induce secondary neutrons that might generate an additional dose to the patient [22] and that it has not been taken into account explicitly when planning or analyzing. All planning objectives criteria and settings were the same for all plans per patient. They can, however, change between the patients due to target size (PTV or GTV depending on diagnosis) and position as well as number of targets. The plans were optimized once before they were normalized and compared. A more comprehensive summary containing all planning criteria and plan details for the different cohorts is available in the supplementary data (Supplementary Tables I and II, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.925578>).

Table I. Summary of patient age (presented as median and range), target volume (presented as median and range), gender distribution and the number of patients in each cohort.

	Brain	H&N	SRS lung	Prostate	SRS multiple Met.	SRS single Met.
No. of patients	20	20	20	20	20	20
Age (years)	59 (31–74)	56 (43–76)	71 (62–88)	69 (54–76)	59 (28–78)	70 (37–84)
Gender (F/M)	4/16	7/13	11/9	0/20	15/5	7/13
PTV (cm ³)	329 (139–553)	548 (322–873)	40 (11–101)	144 (62–177)	7 (2–20)	18 (2–33)

PTV, planning target volume (N.B. PTV equals GTV for brain metastases); SRS, stereotactic radiosurgery.

Analysis and evaluation metrics

The FFF- and STD plans were evaluated with respect to target coverage, dose conformity, homogeneity, treatment delivery time and number of monitor units per prescribed Gy (MU/Gy). Target coverage was evaluated by calculating the percentage of the target volume receiving $\geq 95\%$ of the PD ($V_{95\%}$). Homogeneity index (HI) and conformity index (CI) was calculated according to the definition proposed by others [19]. HI was used to evaluate the plans for high-grade gliomas, H&N and prostate cancer where the aim is to get a homogenous dose to the whole target volume. The CI was used to evaluate stereotactic plans because of the intentional inhomogenous dose distribution. The treatment delivery time (time from first field beam-on to last field beam-off), beam delivery time (treatment time minus the time it takes to get the next beam ready for delivery) and the number of MU/Gy were calculated from the RT plan files exported from our treatment planning system. The datasets were tested for normality (Kolmogorov-Smirnov). Metrics were compared for FFF- and STD plans using Wilcoxon signed rank tests, p -values < 0.05 were considered statistically significant. The standard deviation (SD) was calculated for all plans.

Results

All plans generated were deemed clinically acceptable regardless of treatment technique. As expected, the plans with better target coverage and lower OAR doses tend to have a longer distance between the target volume and OARs. A much more comprehensive and detailed overview of the results is available in the supplementary data (Supplementary Tables III–VIII, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.925578>). None of the datasets were normally distributed, and therefore the Wilcoxon signed rank test was used.

Target coverage, homogeneity and conformity

The data for the target coverage and conformity showed that FFF beam plans, in most cases were dosimetrically equivalent, especially for the smaller target volumes. For larger target volumes the standard flattened beams managed to create better plans using a lower number of monitor units.

The flattened beams resulted in a statistically significant better PTV homogeneity (Figure 1) for high-grade glioma for both 6 MV and 10 MV ($p < 0.001$). The mean HI difference was 1.1% and 1.5% for 6 MV and 10 MV, respectively. The flattened beams also resulted in significantly better HI

for the oropharyngeal cancer cohort for both 6 MV ($p = 0.003$) and 10 MV ($p < 0.001$) with a mean HI difference of 2.4% and 5.4% for 6 MV and 10 MV, respectively. HI (Figure 1) for the H&N patients was calculated using the low risk elective volume because it contains both the high-risk elective volume as well as the tumor volume. For the prostate, lung and intra-cranial metastatic disease patients no significant difference was found for target coverage, conformity and homogeneity (Figure 1).

OARs and healthy tissue

For most OARs the plans were comparable in terms of dose but for the high-grade glioma patients the FFF beams had lower volume of whole brain V_{50Gy} for both 6 MV ($p = 0.048$) and 10 MV ($p = 0.002$) with a mean volume difference of less than 1% for both 6 MV and 10 MV. Even though the differences in dose to the spinal cord were very small (less than 1% for both sites), they were found to be significantly lower using STD beams for H&N while they were significantly lower using FFF beams for SRS lung. The V_{20Gy} to both lungs for SRS lung patients was less than 10% for all patients and no statistically significant difference between STD- and FFF beams for either 6 MV or 10 MV was found. For the prostate patients, Rectum V_{70Gy} and Rectum V_{60Gy} were found to be statistically significant lower for STD10X, however, the mean volume difference was only 0.5% ($p = 0.010$) and 0.6% ($p = 0.030$), respectively. There was no statistical significance found for 6 MV. For the patients with intra-cranial metastatic disease no statistically significant differences were found for the OARs. Regarding the healthy tissue (brain $V_{10-16Gy}$) for single targets SRS brain there was a lower volume receiving 10–16 Gy using FFF10X ($p = 0.001$). However, the total difference for brain $V_{10-16Gy}$ between FFF- and STD plans was less than 0.1% and can most likely be considered as non-significant from a clinical point of view. No statistically significant differences were found for 6 MV.

Delivery parameters

Beam delivery times (denoted as Beam-ON times in Figure 2) were almost identical (within one second) for high-grade glioma and H&N patients. We found that for the patients with higher doses per fraction there was a significantly shorter beam delivery time when using FFF beams. The average beam delivery times for FFF-VMAT was drastically reduced by 55.3% (6 MV) and 75.0% (10 MV) for SRS lung, by 52.1% (6 MV) and 69.7% (10 MV) for SRS multiple metastases and by 56.1% (6 MV) and 69.5% (10 MV) for SRS single metastasis compared to

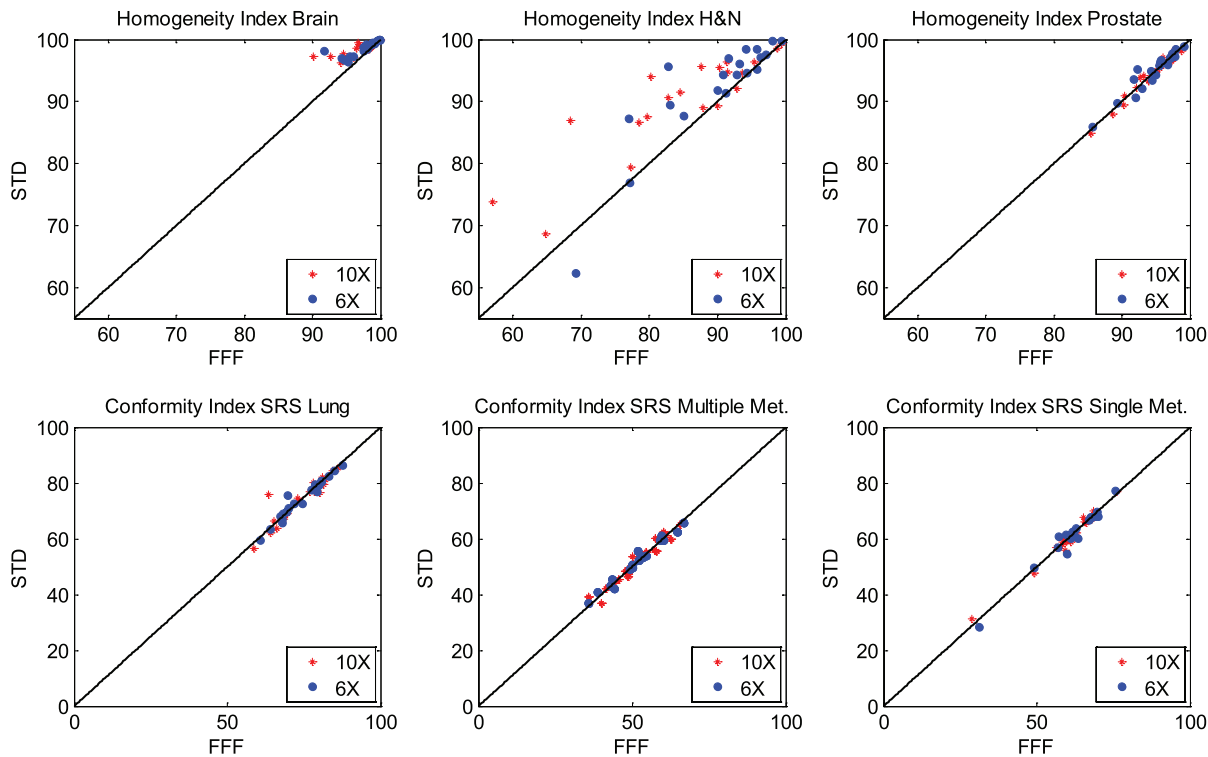


Figure 1. Homogeneity- (brain, H&N and prostate) and conformity (SRS treatments) index for FFF (10 MV and 6 MV) plotted against STD (10 MV and 6 MV) with an identity line. Data points above the identity line represent cases where STD beams are superior and vice versa.

STD-VMAT. For both the high-grade glioma and H&N patients the gantry is able to move at maximum speed ($6^\circ/\text{second}$) so there was almost no difference (less than 0.1%) between the techniques. For

single arc prostate patients there was a small difference of 4.3% (6 MV) and 4.9% (10 MV) faster beam delivery time for FFF beams compared to STD beams.

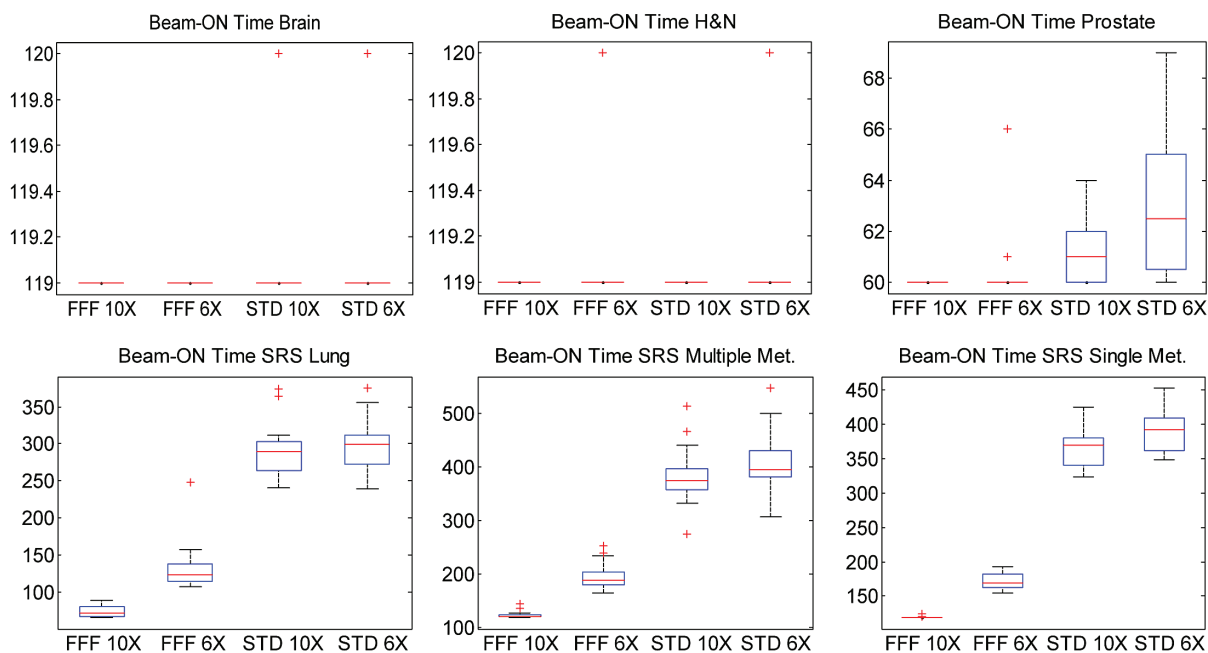


Figure 2. Beam delivery time (seconds) showing median (central red line), 25th and 75th percentiles (blue box) and the whiskers (black-dashed line) which extend to the most extreme data points that are considered non-outliers. The red individually plotted crosses indicate the outliers in the data that are outside $\pm 2.7\sigma$. Observe the time difference on the y-axis; because of the large difference in prescribed dose per fraction, the treatments will undoubtedly differ in treatment time.

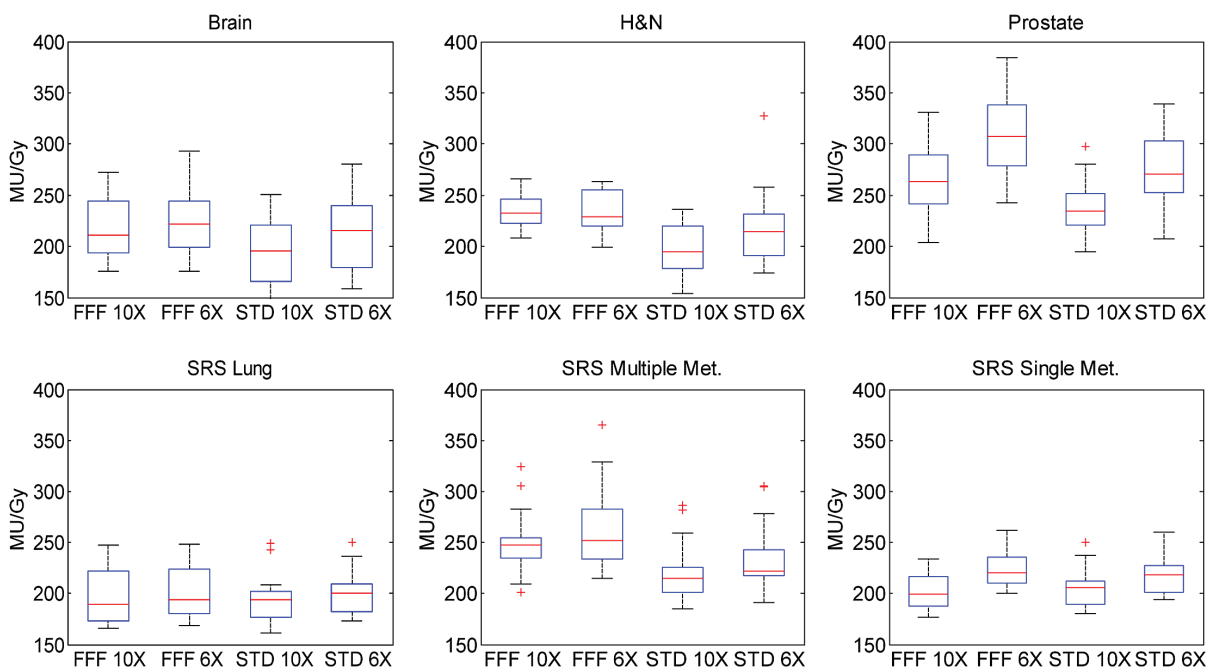


Figure 3. Monitor units per prescribed Gy showing median (central red line), 25th and 75th percentiles (blue box) and the whiskers (black-dashed line) which extend to the most extreme data points that are considered non-outliers. The red individually plotted crosses indicate the outliers in the data that are outside $\pm 2.7\sigma$.

Total treatment times can easily be calculated by adding 25 seconds (the time it takes before the next arc is ready for delivery on a TrueBeam™ STx) between each arc.

The MU/Gy were found to be slightly higher (Figure 3) for high-grade glioma patients for both FFF6X ($p < 0.001$) and FFF10X ($p < 0.001$). The same result was also found for the H&N patients for both FFF6X ($p = 0.003$) and FFF10X ($p < 0.001$). Even though prostate cancer patients with FFF-VMAT had a significantly shorter beam delivery time ($p = 0.002$), the difference was less than 10 seconds. For all diagnoses except SRS lung and 10 MV single target SRS brain there was a significant increase in MU/Gy when using FFF beams. The FFF plans required on average 7% (SD: 2.8%) and 8.4% (SD: 0.5%) more MU/Gy for 6 MV and 10 MV, respectively.

Discussion

FFF beams is a technology that has not yet been implemented, or is currently under evaluation, at radiotherapy centers worldwide. We hope that by presenting an analysis of comparative treatment planning and delivery parameters radiotherapy centers can better prioritize the patients selected for FFF-VMAT. Overall, we found that the treatment plan quality in terms of target coverage and doses to OARs was similar for FFF- and STD-VMAT across all patient cohorts investigated.

However, the target coverage was significantly better for STD-VMAT for larger targets. In addition, we found that the number of MU was significantly larger for FFF-VMAT in general. Further, we found that the treatment time was substantially reduced for stereotactic hypofractionated treatments and that the difference was statistically significant. By means of this analysis of a large patient material allowing for testing for statistical differences, we were able to confirm some and dispute some trends observed in studies involving smaller patient cohorts.

Our data showed that FFF beams in most cases resulted in equivalent plans to STD beams regarding both target coverage and OAR sparing, which is supported by previous works involving fewer patient cases [17,19–21,23,24]. For larger target volumes the FFF technique caused a slight deterioration of the target coverage compared with STD beams. This is a very interesting result since there are previous studies indicating that FFF beams are equal in terms of plan quality compared to STD beams for larger target volumes [19]. Reggiori et al. [17] also found that there was a tendency for FFF beams to be more favorable for medium-sized target volumes while STD beams are more suitable for smaller and larger target volumes. The impacts of target volume size on plan quality found by the earlier studies were, however, not statistically significant and were based on a smaller cohorts patients as compared to the present study. Further, differences in patient material and

details of treatment planning procedure might explain the conflicting findings. Thus, when attempting to find out which patients would be the most suitable candidates for FFF-VMAT it is crucial to include large patient numbers, with clinically representative variation in the location and size of target volumes, as is presented in this study. To our knowledge, no reports were published on the use of FFF-VMAT for high-grade gliomas.

Further, we found that FFF beams require additional MU compared to STD beams, and this is likely because of the conically shaped dose distribution that results in different dose levels between the central and peripheral areas of the field [18]. The increase in MUs counteracts the potential gain in treatment time, as pointed out by Lecher et al. [25]. However, we found that the increase in MUs is almost negligible compared to the substantial increase in dose rate and leading to drastically reduced beam delivery times for treatments with high doses per fraction. Stieler et al. [23] did not observe a significant increase in MU when using FFF and this was explained to depend on the small target volume and large distance to OARs therefore requiring less modulation. This is supported by our data for small and near spherical like targets, such as SRS lung and single target SRS brain that did not show a significant increase in MU/Gy. We did, however, see a significant increase in MU/Gy for 6 MV single target SRS brain. Some of the patients in this cohort did have a small distance to OARs that required additional modulation which might explain the difference.

Several previous published reports [18,20,21] used a small number of patients in their studies which may limit the possibility of appreciate patient-to-patient variability. It can also limit the statistical certainty of the data. The latter can, however, be solved by increasing the number of plans per patient.

A limitation of the present study is that all plans were only optimized once and using the same optimization criteria for both STD- and FFF-VMAT. Potentially, it could be possible to get better plans with both STD- and FFF beams using different optimization criteria. These considerations all need to be addressed to obtain the optimal plan for the individual patient.

In summary, we found that FFF beams were most suitable for small target volumes, treated to high doses per fraction, where a considerable time gain was found while maintaining similar plan quality compared to STD beams. In addition, we found that the target coverage was inferior for the largest volumes for FFF-VMAT, though the differences were quite small.

Declaration of interest: Per Munck af Rosenschöld has research and educational collaboration with Varian Medical Systems, Palo Alto, CA, USA. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Tables I–VIII, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.925578>.