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Flattening Filter Free *vs*. Flattened Beams for Lung Stereotactic Body Radiation Therapy

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Abstract. *Background/Aim: To assess the clinical impact of high dose rate stereotactic body radiation therapy (SBRT) in patients with lung neoplastic lesions. Patients and Methods: From January 2014 to June 2016, a single-center retrospective analysis was performed including all patients treated by either flattening filter free (FFF) beams or flattening filter beams (FF) three-dimensional (3D) SBRT for lung neoplastic lesions. Results: A total of 99 SBRT were performed on 75 patients. Among these, 29 SBRT were performed using a FFF technique while 70 other SBRT were done using a FF technique. Median follow-up time was 12.9 months. Overall, no difference between the two groups was found except for the mean beam on time which was reduced by 3.3 to 0.9 minutes in the FFF group (p<0.001). Conclusion: We report a low toxicity rate and a shortened beam on time in patients treated with 3D FFF SBRT for lung neoplastic lesions.*

The concept of oligometastatic disease state was firstly described by Hellman and Weichselbaum (1). Recent literature data suggested this concept as the state in which patients with cancer have ≤ 5 metastatic or recurrent lesions with active primary lesion (2). Whereas no randomized controlled trial evaluating surgery in the management of patients with lung oligometastatic disease exists, surgical resection of pulmonary metastases is now considered a standard therapeutic procedure and is routinely performed in many departments of thoracic surgery. Indeed, in carefully selected patients, survival was observed up to 33% at 5 years (3, 4).

In general, surgery is believed to offer the best outcomes. However, for medically-inoperable tumors, recent technological advances have led to the emergence of alternative less invasive treatments such as stereotactic body radiotherapy (SBRT) allowing precise delivery of a high irradiation dose defined as "ablative dose" to a target with optimal sparing of normal tissues in few treatment fractions.

For this population, SBRT showed promising results with 2 years local control rates ranging from 66-96% (4-6) and low rate of toxicity. Although metastasectomy remains the standard of care, SBRT became widely used notably for patients unfit for surgery.

SBRT delivery time often lasts long due to high doses per fraction, limited dose rates, application of multiple treatment beams and often usage of intensity-modulated radiotherapy (IMRT) (7). To treat those patients, photon beams usually have a metal filter on their path to make photon fluence uniform (or flat). In order to reduce beam on time, linear accelerators (LINAC) without flattening filter can be used. Indeed, the removal of the flattening filter (FF) leads to a considerable increase in dose rate with non-uniform fluence distribution. The intensity can increase by a factor of 4 to 10. With proliferation of accurate treatment planning algorithms used by SBRT and IMRT, the uniform fluence is no longer a concern. Indeed, several dosimetric studies showed that FFF beams can produce a quite similar treatment plan to flattened beams (8-10). Non-uniform, conical fluence distribution can be solved by IMRT or SBRT while treatment time is lowered leading to less risk of patient movement. Moreover, several authors described that FFF decrease volume receiving low radiation doses suggesting a decrease of stochastic effects (11).

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However, the issue of biological and clinical impact of this technique remains elusive. Indeed, there is a lack of clinical data and only few preclinical studies with contradictory results have been published on the radiobiological effect of FFF treatment (12-17). The aim of this study was to assess efficacy and early toxicity of FFF beams in patients treated for lung tumors.

Patients and Methods

Patient population. We performed a medical chart review of all consecutive patients treated from January 2014 to June 2016 by three-dimensional (3D) SBRT for lung neoplastic lesions at our academic institution (Paoli Calmettes Institute).

Schematically, two different types of lung neoplasms were considered: localized non-small cell lung cancer (NSCLC) and any other primary neoplasms with lung oligometastases (from 1 to 5 metastases). Clinical staging was performed according to the WHO and TNM classifications.

All treatments were discussed at a multidisciplinary tumor board.

Simulation and treatment procedures. All patients were positioned in supine position. To provide an optimal immobilization, vacuum bags were used for all patients whereas abdominal compression was only used for patients presenting medial or inferior tumors. A maximum intensity projection (MIP) image was performed to define the internal tumor volume (ITV). An additional planning target volume (PTV) margin of 3mm (transversal) and 5mm (superior inferior) was further added to account for positioning insecurities.

SBRT planning was performed with Pinnacle® or RayStation® treatment planning software. Irradiation was delivered with an Elekta Versa HD treatment machine using 6MV photons. In March 2015, regarding recent literature data, our department allowed to remove the FF in order to treat patients with high dose rate beam up to 1,200 MU/min. Depending on the stage of disease, a dose ranging from to 40 to 56 Gy was delivered to the 80-82% isodose line with 8 Gy fractions, one fraction a day (rest Saturday and Sunday). In case of proximity to the organs at risk (OAR), reduction of dose per fraction was recommended. The beam number ranged from 9 to 11 depending on tumor and OAR location.

Dose constraints were used for several OAR such as: maximal dose (D_{max}) <37 Gy for esophagus, trachea, principal bronchi, heart, large vessels and brachial plexus; Dmax <21 Gy for spinal cord; mean normal ipsilateral lung (ipsilateral lung-PTV) dose <9 Gy and normal ipsilateral lung V20Gy <15%.

Position verification was systematically applied before each fraction by Cone Beam Computed Tomography being compared with the planning CT.

Follow-up. During the treatment period, patients were followed by a radiation oncologist at least at the end of treatment, 6 weeks, 3 months and 6 months to detect any acute toxicity related to radiotherapy.

Then, long-term follow up was performed every 6 months alternatively by both a radiation oncologist and a medical oncologist. Paraclinical exams were performed at 6 weeks, 3 months, 6 months, 1 year and thereafter every year using ^{18}FDG-CTPET or a CT scan. Response was evaluated by either PERCIST 1.0 or RECIST 1.1 criteria for CTPET and CT scan respectively.

End-points. The primary endpoint of our study was the incidence of early toxicity G ≥2 scored according to the Common Terminology Criteria for Adverse Events, version 4.0. Toxicity was considered as "early" when occurred within 6 months after the radiotherapy start. Secondary endpoints included beam on time, as well as dosimetric variations of target volumes and OAR, and finally oncological outcomes including local recurrence-free survival (LRFS) defined as the time from radiotherapy start to any local failure or death from any cause. Regarding to the low follow up time expected, this study focused on early results for both toxicity and oncological outcomes.

Statistical analysis. Continuous variables were reported as median with corresponding interquartile range (IQR), whereas frequencies and proportions were used for categorical variables. Chi-squared or Student's *t*-test were used to assess quantitative or qualitative variables respectively.

We performed survival analyses by using the Kaplan-Meier method to estimate LRFS. Univariate and multivariate analyses were performed using the Cox proportional hazards model and logistic regression to assess LRFS and toxicity respectively. Finally, a post-hoc power analysis was performed to assess outcomes reliability. For all analyses, a two-side *p*-value <0.05 was considered significant. Statistical analyses were performed using R 3.3.3 software.

Results

Patients and tumors. A total of 99 SBRT were performed on 75 patients with a median age of 72 years (IQR=26-86 years). Among these, 29 (29%) SBRT were performed using a FFF technique while in 70 (71%) others SBRT were done using a FF technique. Median follow up time was 12.6 months (IQR=10.0-14.5 months) and 13.6 months (IQR=7.2-18.1 months) respectively. All patients completed the planned treatment and only 1 patient deceaced before the first follow-up after three months. The study included 34 patients (45.9%) with non-small cell lung cancer, 12 patients (16.2%) with sarcoma, 9 patients (12.2%) with colon adenocarcinoma, 6 patients (8.1%) with endometrial cancer and 15 patients (20.3%) with other primary neoplasms. Tumor stages were as follows: 10 stage I (13.5%), 2 stage II (2.7%), 11 stage III (14.9%) and 51 stage IV (68.9%). No significant difference was observed between the two populations. Patients and tumors characteristics are detailed in Table I.

Cancer treatment. About patients treated with FFF beams modality, median dose delivered to the PTV was 48 Gy (IQR=40-48 Gy) with a median dose per fraction of 8 Gy (IQR, 6-9 Gy). The mean GTV and PTV volumes were 21.1cc and 43.8cc respectively. Regarding the OAR, the mean ipsilateral lung V30Gy, V20Gy and ipsilateral mean lung dose were 7.2%, 13.0% and 9.0Gy respectively. The mean of the total monitor units delivered was 1076.6 corresponding to a mean treatment delivery time of 0.9 min. About patients treated with FF beams modality, median dose

Table I. *Baseline characteristics of the study population.*

	Total sample N=75 (100%)	FF n=54 (72%)	FFF n=21 (28%)	*p*-Value (FF VS FFF)
Gender (male/female), N (%)	43 (57.3%)/32 (42.7%)	30 (55.6%)/24 (44.4%)	13 (61.9%)/8 (38.1%)	0.618
Age, median (IQR)	71 (60-77)	71 (64-78)	67 (58-72)	0.661
Performance Status, median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.25
Histology, N (%)				0.891
NSCLC	33 (44.0%)	23 (42.6%)	10 (47.6%)	
Sarcoma	13 (17.3%)	9 (16.7%)	4 (19.0%)	
Colon adenocarcinoma	9 (12%)	7 (13%)	2 (9.5%)	
Endometrial cancer	5 (6.7%)	3 (5.6%)	2 (9.5%)	
Other	15 (20%)	12 (22.2%)	3 (14.3%)	
Stage, N (%)				0.894
I	10 (13.3%)	7 (13.0%)	3 (14.3%)	
II	2 (2.7%)	1 (1.9%)	1 (4.8%)	
III	12 (16%)	9 (16.7%)	3 (14.3%)	
IV	53 (70.7%)	39 (72.2%)	14 (66.7%)	

FFF: Flattening filter free; FF: flattened filter; IQR: interquartile range; NSCLC: non-small-cell lung carcinoma.

Table II. *Treatment parameters (mean±DS).*

	Total sample N=99 (100%)	FF n=70 (71%)	FFF n=29 (29%)	*p*-Value (FF VS FFF)
Dose to PTV (Gy)	43.7±5.0	43.7±5.4	43.7±4.3	0.993
PTV (cm^3)	41.6±39.7	40.1±39.9	43.8±40.3	0.741
GTV (cm^3)	17.4±26.8	14.5±23.5	21.1±30.7	0.419
Ipsilateral lung V30Gy (%)	7.1±5.2	7.1±5.5	7.2±4.8	0.952
Ipsilateral lung V20Gy (%)	12.9±8.1	12.9±9.2	13.0±6.4	0.969
Ipsilateral MLD(Gy)	8.2±5.5	7.7±4.1	9.0±7.1	0.414
Total monitor units	1394.5±522.0	1525.4±566.1	1076.6±125.3	<0.001
Beam on time (min)	2.6±1.6	3.3±1.3	0.9±0.1	<0.001

SD: Standard deviation; PTV: planning target volume; GTV: growth target volume; FFF: flattening filter free; FF: flattened filter; VxGy: volume receiving more than x Gy; MLD: mean lung dose.

delivered to the PTV was 48 Gy (IQR, 40-48 Gy) with a median dose per fraction of 8 Gy (IQR, 5-10 Gy). The mean GTV and PTV volumes were 17.4cc and 41.6cc respectively. Concerning the OAR, the mean ipsilateral lung V30Gy, V20Gy and mean lung dose were 7.1%, 12.9% and 7.7% respectively. The mean of the total monitor units delivered was 1,525.4 corresponding to a mean treatment delivery time of 3.3 minutes.

No significant difference was observed between the two populations except for the total monitor units delivered and the treatment delivery time. Treatment characteristics are shown in Table II.

Toxicities. Most in-field toxicities were mild to moderate. No grade ≥3 acute toxicity was observed in the two groups. Only 5 (17.2%) and 3 (10.3%) patients experienced grade ≥1 and grade ≥2 acute toxicities in the FFF beams group *versus* 19 (27.1%) and 10 (14.3%) patients respectively in the FF group. Regarding late toxicities, one patient experienced grade 5 toxicity at 8 months of follow-up due to a hemoptysis caused by a bronchial necrosis. He was treated by FF beam modality delivering 42 Gy (7 Gy per fraction). No other grade ≥3 was observed in the two groups. Seventeen (24.3%) and 12 (17.1%) patients experienced grade ≥1 and grade ≥2 late toxicities in the FF beams group *versus* 5 (17.2%) and 1 (3.4%) patients respectively in the FF group.

A combination of clinical and dosimetric factors was tested for toxicity grade 2 or higher: the use of FF, planning target volume (PTV), prescribed dose, dose per fraction, OMS status and the volume receiving 20 Gy or more. Only the number of fractions was significantly associated with toxicity in both univariate and multivariate analysis. The associated OR was 1.7 (95%CI=1.02–3.12, p=0.046) and 1.7

Table III. *Factors associated with a risk of toxicity and local failure.*

Variable associated with grade ≥2	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
FFF	0.69	0.15-2.48	0.60	0.74	0.15-2.76	0.67
Number of fractions	1.74	1.02-3.16	0.047	1.72	1.02-3.09	0.05
PTV	1.00	0.99-1.02	0.40	-	-	-
Prescribed dose	1.10	0.96-1.29	0.21	-	-	-
V20Gy	1.01	0.90-1.10	0.89	-	-	-
Performans status	1.99	0.47-10.08	0.38	-	-	-
Age	1.02	0.97-1.1	0.50	-	-	-
Variable associated with LRFS	**Univariate analysis**			**Multivariate analysis**		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
FFF	0.69	0.19-2.51	0.57	0.37	0.07-1.88	0.23
PTV	1.01	0.99-1.02	0.13	1.01	0.99-1.02	0.11
Prescribed dose	0.95	0.87-1.05	0.33	0.98	0.85-1.12	0.8

PTV: Planning target volume; FFF: flattening filter free; FF: flattened filter; VxGy: volume receiving more than x Gy; LRFS: local recurrence-free survival.

(95%CI=1.01-3.01, p=0.05) respectively. Factors associated with toxicity grade ≥2 are reported in Table III.

Patterns of relapse. During the follow-up period, 3 (10.3%) lesions relapsed in the FFF beams group *versus* 10 (14.3%) in the FF group. The median time to recurrence was 4.5 months (IQR, 3.1-4.5 months) and 8 months (IQR, 3,1-14,1 months) respectively. Metastatic recurrences occurred in 13 (44.8%) and 41 (58.1%) patients, respectively.

Survival times. During the follow-up period, 10 (14.3%) patients deceased, including 9 (12.9%) from the disease, 3 (14.3%) and 7 (14.2%) in the FF and FFF group respectively. The 1 year LRFS rate was 86.1% (95%CI=77.6-95.6%) and 89.7% (95%CI=79.2-100%) respectively (Figure 1).

A combination of clinical and dosimetric factors was tested for LRFS: the use of FF, planning target volume (PTV), prescribed dose, number of fractions, and the OMS status. No factor was significantly associated with LRFS in both univariate and multivariate analysis. Factors associated with LRFS are reported in Table III.

Discussion

Very few data are available on the safety of FFF beams for lung SBRT, however the rational to use it is the possibility to deliver high ablative doses faster and more precisely, due to decreased out-of-field dose and to increased dose rate removing flattening filter. In one hand, shortening of treatment time improves patient comfort especially in elderly and frail patients and was shown to improve patient stability (18-20). On the other hand, it may introduce novel hazards, *e.g.* in case of patient or organ movement there is less time to intervene. There are also dosimetric uncertainties due to the interplay effect; *e.g.* Ong *et al.* investigated the dosimetric impact of intrafractional motion during treatment and found an increased sensitivity of the target coverage and dose if FFF beams are used compared to flattened beams (7). But the major issue is probably the unknown radiobiological hazard of using high dose rate beams.

Possibly, it is due to these reasons that the use of FFF beams is not the standard of care for a large part of the radiation oncologists' community. Indeed, if many dosimetric data showed that FFF beams can produce quite similar treatment plan than with flattened beams (8-10), there is a lack of pre-clinical and clinical studies. To our knowledge, only two studies have found a significant difference in clonogenic cell survival between FF and FFF treatments suggesting a slightly increased radiobiological effect in cells treated with high dose rate radiation (12, 16). However, in the study published by Steenken *et al.* the authors conclude that the slight difference observed is unlikely to result in clinically relevant differences in outcome. Several other studies failed to show any difference in clonogenic cell survival between the two types of treatment (13-15, 17).

In the present study, safety and early local tumor control of patients treated with 3D SBRT and FFF beams for lung

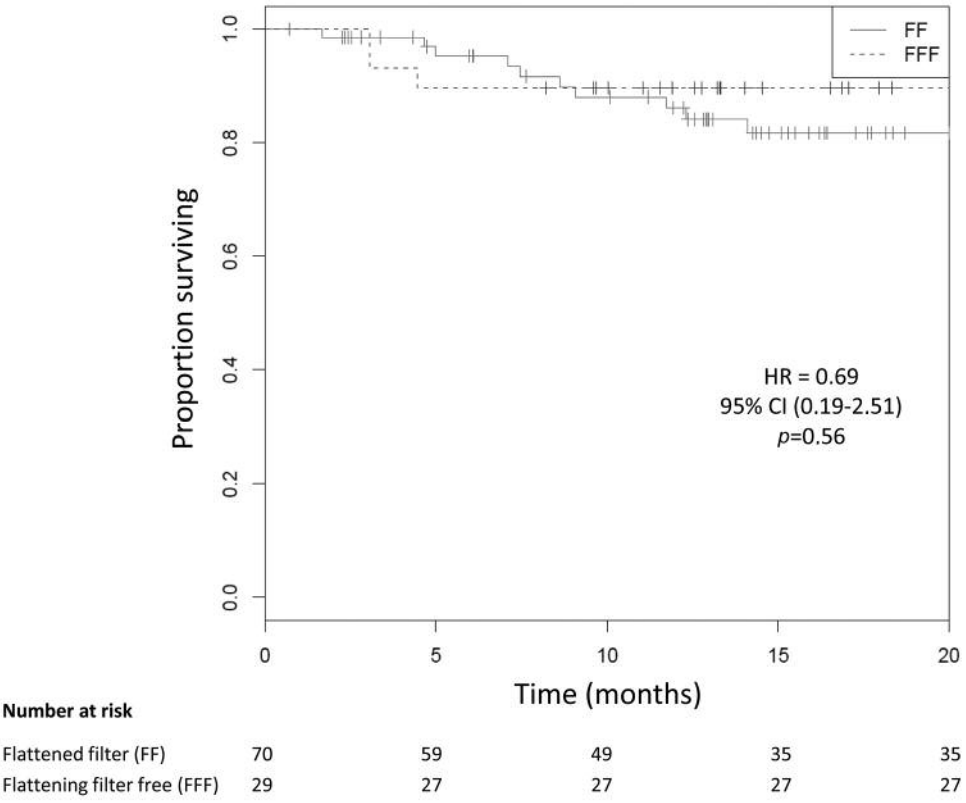

Figure 1. *Kaplan–Meier estimated local recurrence-free survival.*

neoplastic lesions were assessed. Both lung primary and secondary neoplasms were included because we aimed to analyze overall patient safety, detect any unexpected toxicity and local control failure rather than evaluating overall survival of a specific population. Overall, no significant difference was observed for toxicity between the two groups. In general, toxicity was low with only 3 patients (10.3%) suffering from acute grade 2 or higher side-effects in the FFF group *vs*. 10 (14%) in the FF group. No acute grade ≥3 was observed. No factor was significantly associated to toxicity grade ≥2 except the number of fractions. This confirms the need to increase dose fractionation in patients at risk (large PTV, proximity of OAR, *etc*.).

As far as we know, only three other retrospective studies focused on FFF beams for thoracic SBRT.

Navarria *et al*. reported results in patients treated with SBRT for medically-inoperable early-stage non-small cell lung cancer. All the 86 patients receiving FF beams were treated with 3D technique whereas all the 46 patients receiving FFF beams were treated with VMAT Rapid Arc technique. In the FFF group, 17% and 4% of patients experienced grade ≥2 and grade 3 pulmonary toxicity respectively, no difference was observed between the two groups. Interestingly, they observed a significant earlier radiological response in the FFF group with a 1 year local control rate of 100% *vs*. 92.5% in the FF beams group (p=0.03) (21). Yet, the difference observed between the two groups could be caused by other factors such as the use of a different technique in the FFF arm (VMAT). Furthermore, Prendergast *et al*. identified 64 patients treated using IMRT unflattened photon beams for lung lesions. Among a subset of 49 patients with greater than 90 days follow up (median=11.5 months), 14 (28.6%) experienced a toxicity grade ≥2 and 1 deceased from severe pneumonitis (22). Finally, early results of 61 pulmonary lesions treated with SBRT in FFF-mode were assessed in the study by Rieber *et al*., who reported only 5% rate of early grade ≥2 side-effects and a one-year local progression-free survival of 92.8% (23).

Regarding oncological outcomes, the estimated 1-year LRFS rate in our study was 86.1% (95%CI=77.6-95.6%) and 89.7% (95%CI=79.2-100%) in the FFF and FF group respectively.

These similar outcomes between the two groups are consistent with the other clinical and pre-clinical studies suggesting a low impact of FFF beams on radiobiological effects and clinical goals. However, our outcomes are based on retrospective data and a low number of patients, which makes difficult to draw any definitive conclusion. Though, even if our study was not powered for efficacy goals, the post-hoc power analysis of this study to detect a 20% difference on the primary end point (acute grade ≥2 toxicities) reached 68%. Regarding the early effects grade 3 or higher, the estimated post-hoc power to detect a 10% difference was 69%. Therefore, these data showed relatively reliable arguments regarding the safety of FFF beams. Another limitation of our study was that the low number of events limited multivariate analysis capabilities, especially regarding the number of variables included in the model. Finally, our follow-up time was not long enough to properly analyze late toxicity.

Conclusion

We report on a shortened beam on time and a low early toxicity rate in patient treated with 3D FFF SBRT for lung neoplastic lesions. Our study was in range with clinical and pre-clinical data suggesting a low biological impact of high dose rate irradiation although longer follow-up is needed to confirm these results.

Conflicts of Interest

The Authors declare no competing financial interests.

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