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SBRT in lung cancer

Parenchymal lung changes on computed tomography after stereotactic radiotherapy using high dose rate flattening filter free beams

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ABSTRACT

Flattening filter free (FFF) beams allow fast delivery of stereotactic radiotherapy. To evaluate biological effects of FFF in lung, we compared parenchymal changes after FFF and non-FFF stereotactic volumetric modulated arc therapy. Standardized multi-observer consensus evaluation of follow-up CT scans revealed no major differences between FFF and non-FFF.

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High dose rate flattening filter free (FFF) radiotherapy beams, with a maximum dose rate of 2400 monitor units/minute (MU/min), compared with a more conventional 600 MU/min, have recently entered clinical practice, allowing reductions in treatment time for high dose per fraction stereotactic body radiotherapy (SBRT) [1,2]. These beams are associated with short beam-on times [2], high average [3] and very high instantaneous dose rates [4], all of which has stimulated interest in whether or not their radiobiological effects differ from lower dose rate flattened beams [4]. A similar debate occurred when intensity modulated radiotherapy (IMRT) began to be used in place of 3-dimensional conformal radiotherapy, except that at that time, the discussion centered on the prolonged delivery times associated with IMRT [4,5]. There is limited pre-clinical data available on the in vitro effects of FFF/very high dose rate beams on cultured cell lines. Most of the available publications focus on tumor cells and some of the results are conflicting [6–9]. Although there are reports suggesting no deleterious effects from high dose rate FFF irradiation on non-cancer (V79 Chinese hamster lung fibroblast) cell lines [8–10], in vivo data are needed to support this. This has been acknowledged by some authors [4,9], one reason being that there may be differences between in vitro and in vivo cells [11]. Since our first patient was treated using FFF beams approximately 3 years ago, the technique has become routine and is now used in a significant proportion of our SBRT program, including large fraction lung treatments [2]. Given the limited in vivo data that have so far been reported concerning normal tissue effects of FFF beams, we undertook a retrospective study to evaluate parenchymal lung changes in patients treated with FFF lung SBRT. We have previously used the pattern of computed tomography (CT)-based lung changes as a bio-marker for radiation effects on the lung [12,13].

Materials and methods

We previously reported on the parenchymal lung changes after lung SBRT delivery using fixed non-coplanar, flattened conformal beams [12], and have compared these with the changes after lung SBRT delivered with flattened beam coplanar volumetric modulated arc therapy (VMAT) [13]. The previously published data for flattened beam RapidArc® (Varian Medical Systems) VMAT delivered at 600 or 1000 MU/min [13] was used as a benchmark (RA group, $n = 29$ patients) in the present study, and we compared it to CT-based lung changes in 44 consecutive patients treated with FFF lung SBRT (maximum dose rate of 2400 MU/min; RA-FFF group). Eligible patients were identified using institutional databases, and had to have at least one follow-up CT scan performed approximately 3 months after treatment, and follow-up scans in our institution. As in our previous studies, a published, standardized nomenclature for describing early (<6 months after treatment) and late (⩾6 months after treatment) CT lung changes was used [12,13]. In brief, early CT changes were described as

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patchy (<5 cm) ground glass opacity (PGGO); diffuse (⩾5 cm) ground glass opacity (DGGO); patchy consolidation (PCO); diffuse consolidation (DCO) or no evidence of increased density (NID). Late changes were described as modified conventional; mass-like fibrosis; scar-like fibrosis or no evidence of increased density. A consistent method of CT evaluation has been used in prior studies and was also used in the present analysis. This includes: discussion- based consensus evaluation by 3 physicians (2 of whom have participated in all 3 scoring studies); a separate person recording the decision and projecting the scans; all scans projected onto a large screen, that can be seen by all the physicians at the same time; use of software that can facilitate easy comparison of serial scans; all physicians provided with a sheet describing the early and late scoring systems [12].

The FFF treatments were delivered on a TrueBeam™ platform (Varian Medical Systems). Non-FFF treatments were delivered on a Novalis Tx™ (Varian Medical Systems and Brainlab AG). Higher dose/fraction treatments (e.g., 3 fractions of 18 Gy or 5 fractions of 11 Gy) are now preferentially delivered with FFF [2]. The approach to treatment planning was the same in both groups. This has been previously described, and is briefly summarized here [2,12,14]. The Eclipse treatment planning system (Varian Medical Systems) was used, with the anisotropic analytical algorithm (AAA) and 2 coplanar arc RapidArc, with dose calculation performed on the average intensity projection dataset and effort made to spare the contralateral lung during optimization. FFF treatments were delivered with a 10 MV beam and flattened treatments with 6 MV. All internal target volumes (ITV) were delineated on the average intensity projection dataset, using information from a 10-phase free-breathing 4-dimensional CT scan. The planning target volume (PTV) was an isotropic 5 mm expansion of the ITV. Treatment was delivered in free-breathing using cone-beam CT for target-based set-up prior to irradiation. The prescription dose was prescribed to the 80% isodose and the plan was normalized so that 95% of the PTV was covered by the prescription dose.

Follow-up CT scans were performed as per the institutional protocol – approximately 3, 6 and 12 months after treatment, and then at least yearly [15]. For the purposes of this study, the follow-up scans and the planning CT scans were all imported into Velocity AI™ (Velocity Medical Solutions and Varian Medical Systems) to allow for easy comparison on the projected screen (Samsung 650TS-2).

Statistical analysis

Baseline and treatment characteristics of the RA and RA-FFF groups were compared using Chi-square test (dichotomous variables), Independent samples *t*-test (continuous normally distributed variables), Fisher's exact test (categorical variables) or Mann–Whitney *U* test (ordinal variables). The distribution of early radiologic changes was compared between RA and RA-FFF groups with the Chi-square test using the first scan of each patient (all within 6 months of start treatment). Differences in the proportion of late (at least 6 months after start treatment) radiologic changes rated as a modified conventional pattern were compared between RA and RA-FFF using Generalized Estimating Equation (GEE) analysis. The dichotomous outcome variable was whether the change was rated as modified conventional or not. Technique (RA or RA-FFF) was included as an independent variable in the model. An exchangeable correlation structure was assumed to take into account within-patient dependence of the outcome. Robust model-based estimates of the proportion of late radiologic changes rated as modified conventional were calculated for each of the techniques together with their 95% confidence interval.

Results

The baseline characteristics of the two groups are summarized in Table 1. These were generally similar, but there was a difference in the proportion of smokers, and the number of fractions delivered.

When the changes on the first follow up scan were assessed, no statistical differences were seen in the distribution of early changes in the 2 groups. The proportion of NID/PGGO/DGGO/PCO/DCO was 34.5/17.2/17.2/13.8/17.2% and 38.6/6.8/6.8/11.4/36.4% for the RA and RA-FFF groups respectively ($p = 0.21$, Chi-square test). The timing of the first scan was comparable, with a median 3.4 and 3.3 months and interquartile range 3.2–3.7 and 3.1–3.5 months, for the RA and RA-FFF groups respectively ($p = 0.28$, Mann–Whitney U test).

Table 1
Comparison of baseline characteristics between the groups treated with RapidArc (RA) and RA flattening filter free (RA-FFF) techniques.

	RA ($N = 29$)	RA-FFF ($N = 44$)	*p*-value
Gender (*N*, % male)	19/28 (67.9)[a]	23/44 (52.3)	0.19[b]
Age at first fraction in years (mean, SD)	69.5 (7.9)	70.0 (9.2)	0.82[c]
History of smoking (*N*, % yes)	29/29 (100)	31/37 (83.8)[a]	0.03[d]
Peripheral or central (*N*, % peripheral)	23/29 (79.3)	36/44 (81.8)	0.79[b]
Diameter tumor in mm (median, IQR)	25.0 (18.5–31.5)	19.25 (15.3–31.8)	0.37[e]
FEV absolute (median, IQR)	2.20 (1.28–2.95)[a,N=25]	1.58 (1.31–2.37) [a,N=28]	0.26[e]
PTV in cm^3 (median, IQR)	25.8 (18.2–41.6)	19.9 (14.6–55.2)	0.55[e]
Dose rate in MU/min (*N*, %)			
600	10 (34.5)	0 (0)	
1000	19 (65.5)	0 (0)	
2400	0 (0)	44 (100)	
Total dose (Gy)	55 (54–60)	55 (54–60)	0.05[e]
Fractions (*N*, %)			0.04[e]
3	8 (27.6)	19 (43.2)	
5	11 (37.9)	20 (45.5)	
8	10 (34.5)	5 (11.4)	

N = number, SD = standard deviation, mm = millimeters, cm^3 = cubic centimeters, IQR = interquartile range, MU/min = monitor units/minute, Gy = Gray.
[a] Missings excluded.
[b] Chi-square test.
[c] Independent samples *t*-test.
[d] Fisher's exact test.
[e] Mann–Whitney *U* test.